Asymmetric hydrogenation and hydroformylation of 1,1-disubstituted olefins

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Index

1 Introduction and task formulation

Chirality is the property of an object that does not allow to result in itself after implementation of any symmetry operation. Two enantiomers[i] of a chiral object, for instance a chiral molecule, behave to each other like an image and a mirror image (Figure 1).

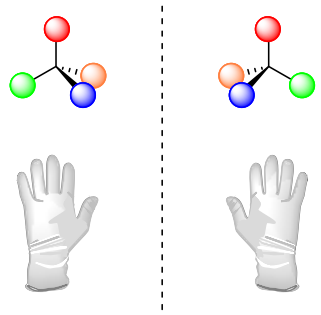


Figure 1. Chirality of a molecule: both compounds behave to each other like an image and a mirror image and cannot be aligned.

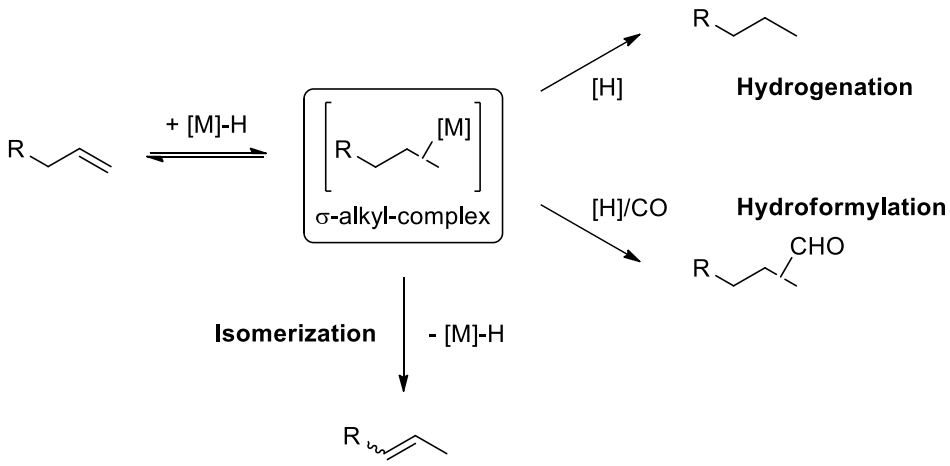
When a prochiral compound is transformed into a chiral one, both enantiomers can be formed.[ii] They have same physical and chemical properties like melting point, boiling point or solubility,[iii] but they have the characteristic to rotate linear polarized light with the same amplitude but to opposite directions. When enantiomers interact with other chiral compounds, diastereomers are formed. However, these diastereomers have different physical and chemical properties. Everywhere in living nature consisting mainly of homochiral compounds, the formation of such diastereomers plays a crucial role. Typical examples are the interaction of chiral aroma compounds with chiral receptors in the human nose (mainly proteins) or the effect of chiral pharmaceuticals on any biological chiral receptors in the body. Another example is the interaction of chiral agrochemicals with chiral receptors in plants. An instance of a chiral drug, in which both enantiomers have different therapeutic effects, is illustrated in Figure 2. Darvon is an analgesic agent; its enantiomer Novrad has an antitussive effect.

Figure 2. Enantiomers and their different properties: Darvon and Novrad.

This situation has led to a revolution in the pharmaceutical industry, because now the individual effect of each enantiomer has to be tested and proved.[iv] With the help of the eudismic ratio,[i] statements about

[i] These are compounds with the same chemical constitution, but they cannot be aligned due to a different physical configuration.
[ii] The 1:1-mixture of two enantiomers is called “racemate” or “racemic mixture”.
[iii] Noteworthy, at a level of very small energies, differences of about 10^{-14} J/mol have been calculated, which is one possible rationalization for the development of homochirality on earth.[1]
[iv] The discussion about the effect of both enantiomers of thalidomide was crucial for this consideration.

the pharmacological activity of the mixture of both enantiomers of a drug can be made. It also explains why it is often so important to prepare exclusively one stereoisomer.
There are many different opportunities to obtain enantiomerically pure compounds, which proved to be successful in recent years. One of the oldest but still powerful method is **resolution** of diastereomers. Starting from the produced racemic mixture, both enantiomers are converted into diastereomers with the help of enantiomerically pure chiral excipients.[ii] These diastereomers can be separated by crystallization or chromatography. The corresponding pure enantiomer is finally yielded by separation from its excipient. Unfortunately, the maximum yield of the desired enantiomer can only reach 50 %, because usually one form is needed and the other is unwanted (waste).
It is spoken of the **chiral pool** when naturally occurring chiral building blocks are used to constitute the desired optically pure compounds. However, these compounds are limited to their natural occurrence and fixed configuration of the starting material.
The stoichiometric asymmetric synthesis utilizes a chiral **auxiliary**[iii] that enables the substrate to be bound and consequently converted diastereoselectively. After separation from the auxiliary, the desired product occurs enantiomerically pure. But, this way is often uneconomical, since stoichiometric amounts of a chiral excipient are required and its separation turns out to be problematic.
The most effective method for the preparation of enantiomerically pure compounds is **asymmetric catalysis**. With the help of a relatively small amount of a chiral catalyst (e.g. enzyme, metal complex etc.), substrates can be converted into one required enantiomer with excellent stereoselectivity. Supplementary, mild and thus economical reaction conditions make an application on industrial-scale very attractive.
Enantioselective hydrogenation as well as enantioselective hydroformylation are two important kinds of catalysis to obtain enantiomerically pure compounds. Depending on the reagent, they undergo different pathways in their catalytic cycles, as illustrated in Scheme 1.



Scheme 1. Starting from the olefin, the σ-alkyl-metal-complex is formed by addition of the catalyst. This complex reacts either with hydrogen to yield an alkane (hydrogenation) or with carbon monoxide and hydrogen to generate an aldehyde (hydroformylation). In the case of β-hydride elimination, isomerization occurs.

The σ-alkyl-metal-complex is considered as a pivotal intermediate for the whole dissertation. It can react with hydrogen to form the saturated compound. Reaction with syngas leads to the aldehyde.

[i] The eudismic ratio describes the difference in the pharmalogical activity of both enantiomers in a drug. It represents the quotient of the activity or affinity of the pharmacological effective enantiomer (eutomer) to the activity or affinity of the less or non-effective enantiomer (distomer).
[ii] Usually chiral excipients are compounds of natural origin, for instance tartaric acid, sugars, alkaloides, etc.
[iii] A chiral auxiliary is a chemical compound, what is incorporated into a reaction to control the stereoselectivity. After completion of the reaction the auxiliary is separated from the product and can be reused.

β-Hydride elimination affords the isomerized olefin. By application of prochiral compounds, hydrogenation and hydroformylation, respectively, give rise to chiral products.
Despite of the usage of different reaction gases (hydrogen and a mixture of carbon monoxide and hydrogen [e.g. syngas]) and of leading to different reaction products (alkanes and aldehydes), enantioselective hydrogenation and enantioselective hydroformylation have following similarities:

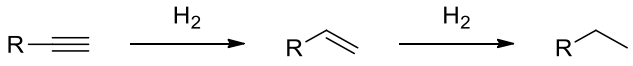
- metal catalysts are used (e.g. rhodium, ruthenium, cobalt, iridium, palladium)
- olefins are used as substrates
- chelating chiral phosphorus ligands (especially trivalent phosphorus compounds) are used
- high enantioselectivities can be reached
- high atom economy: small molecules are added and practically no waste is produced
- hydrogenation can occur as a side reaction accompanied by the hydroformylation

These facts make clear that both ways of catalysis are of special interest for synthesis chemists, because starting from the same substrates a vast variety of products can be achieved by minor changes of reaction conditions.
The task of this dissertation was to test and explore the ability to hydrogenate and hydroformylate 1,1-disubstituted olefins and to reach a significant enantiomeric excess (ee) of the resulting chiral products. **The particular challenge was that substrates chosen herein were seldom or never in the focus of asymmetric catalysis.** The results should be optimized by varying the reaction conditions and by the synthesis and application of novel chiral ligands. Thus, the goal was to find elegant or alternative routes to a range of enantiomerically pure compounds by catalysis.

2 General section

2.1 Hydrogenation

Hydrogenation, in general, is the addition of hydrogen to a multiple (double or triple) bond of an organic molecule in the presence of a catalyst (Scheme 2).



Scheme 2. Hydrogenation of alkynes to alkenes and finally to alkanes.

It is not necessarily limited to carbon-carbon multiple bonds, but also for carbon-heteroatom multiple bonds, e.g. carbon-nitrogen and carbon-oxygen bonds. As a hydrogen source molecular hydrogen is usually applied, but other hydrogen donors (isopropanol, formic acid derivatives) have been utilized in transfer hydrogenation. The H-H bond energy is 434 kJ/mol,[2] therefore a catalyst is required to lower the dissociation energy. Usually, it is distinguished between heterogeneous and homogeneous hydrogenation. While for heterogeneous hydrogenation the catalyst is not soluble in the reaction medium and at least two phases exist, the latter is characterized by existence of the catalyst and the substrate in one phase.[i]

On a large industrial-scale, the heterogeneously catalyzed hydrogenation is of greater importance compared to the homogeneous. However, when stereoselectivity is aimed in a reaction, homogeneous catalysis is the first choice.[3] This preference can be rationalized by the better reproducibility of molecular defined catalyst preparation and reaction. Depending on the nature of the substrate and on the choice of the catalyst, the homogeneously catalyzed hydrogenation can be divided into an asymmetric and non-asymmetric version.

2.1.1 Principles and generals

Asymmetric hydrogenation is meant when a prochiral substrate (e.g. olefin, ketone or imine) is transferred into a saturated chiral product with formation of at least one stereogenic center. As catalysts a wide range of transition metal complexes have been used. Rhodium, ruthenium and iridium are proved to be especially powerful for this purpose.

Polar groups, located next to the double bond, are beneficial for the asymmetric hydrogenation of olefins since such groups allow an efficient electronic and steric stereodifferentiation.[ii] On the other hand, such heteroatoms may additionally coordinate to the metal center. As a result, chelates are formed, which further reduce the conformational flexibility.

1,1-Disubstituted, 1,1,2-trisubstituted (internal) and 1,1,2,2-tetrasubstituted olefins can be hydrogenated enantioselectively. The mechanism for the Rh-catalyzed hydrogenation of 1,1-disubstituted olefins[5] differs from the Ru-catalyzed hydrogenation in the manner of the addition of hydrogen as shown by Noyori for the example of prochiral (2-acetamidomethyl)acrylate (MAA).[5a]

[i] It should be taken into consideration that a system consisting of a gas and a liquid also represents a two-phase system, which should be assigned to heterogeneous catalysis. Usually, this differentiation is not done in catalysis.

[ii] However, there are some examples of the successful Ir-catalyzed enantioselective hydrogenation of unfunctionalized substrates. Unlike Rh- and Ru-diphosphine-complexes they do not require the presence of a coordinating group near the C=C bond, so even purely alkyl-substituted olefins could be hydrogenated with high enantioselectivity. Recent works were published by Pfaltz, Andersson and Diéguez.[4]

In principle, both enantiomers can be yielded equally. What stereoisomer is favored most can be qualitatively explained with the stereodifferenting manner of coordination of the substrate to the catalyst. With the help of the *quadrant rule*,[6] the favorable orientation of the coordinated olefin is concluded. This can be clarified with the example of (*R*,*R*)-Me-DuPhos, a diphosphine in which two phosphorus atoms are part of a chiral phosphacycloalkane. The phosphine units are connected by an achiral scaffold.[7] If one imagines the rhodium catalyst bearing the bidentate ligand and divide it into four quadrants, both methyl groups of each ring can be assigned to one quadrant (Figure 3).

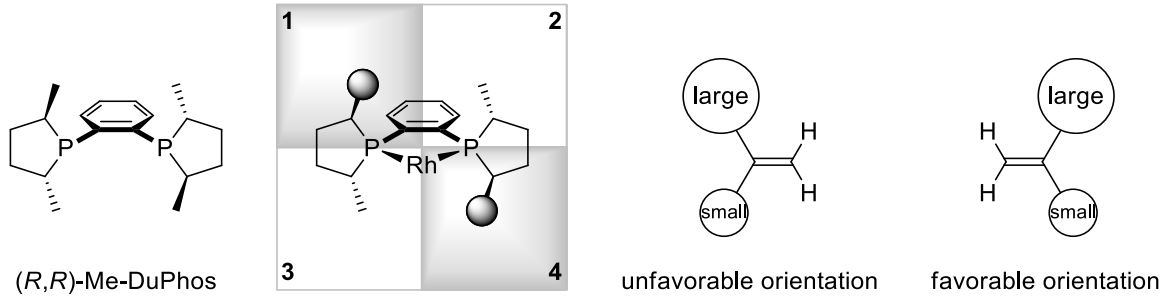


Figure 3. (*R*,*R*)-Me-DuPhos, the *quadrant rule* of the ligand coordinated to rhodium and the two orientations how the substrate can coordinate.

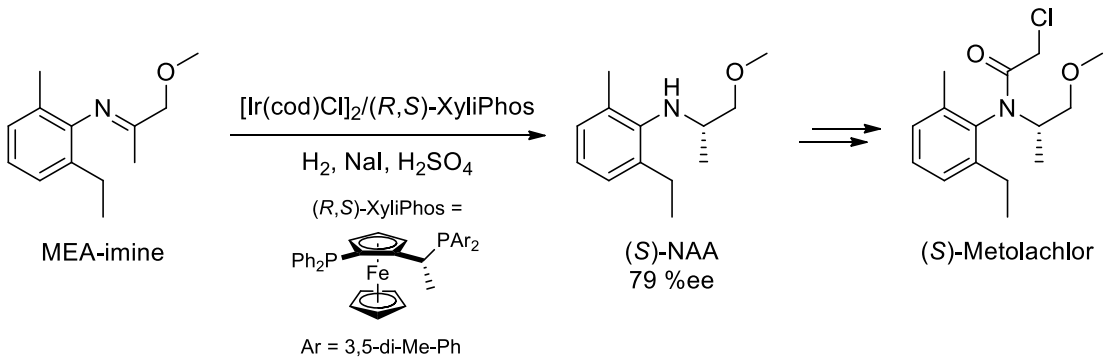
In the case of (*R*,*R*)-Me-DuPhos, *quadrant 1* as well as *quadrant 4* are "occupied"; the two others are "empty". Depending on what side the substrate approaches, two diastereomers can be formed.[i] In a consequence, steric repulsion is minimized when the substrate coordinates in such a way that larger substituents do not interact with one of the blocked quadrants. Thus, only one substrate-complex is favored that finally leads to a single enantiomer. However, this model does not explain why more steric hindered ligands do not mandatorily generate highest enantioselectivities for a substrate.
A quantitative concept, derived from kinetic investigations, is the famous Halpern-mechanism,[ii] which differentiates between two diastereomeric catalyst-substrate-complexes.[8] This so-called major-minor concept is based on the assumption that both diastereomers are formed at the beginning of the catalytic cycle: the thermodynamically favored (major) complex and the thermodynamically unfavored (minor) complex. Since the former is much more stable toward the reaction with hydrogen, it reacts more slowly to the corresponding enantiomeric product than the latter. In the result, the predominantly formed enantiomer derives from the minor-pathway.[5a,8]

2.1.2 Enantioselective hydrogenation of olefins in industry

Up to now, a large number of large- or small-scale processes, applying asymmetric hydrogenation, have been conducted in industry.[9] Until 2012, the synthesis of chiral Metolachlor,[iii] one of the most important grass herbicides for use in maize, represented the largest process for asymmetric catalysis (Scheme 3).[10]
The stereoselective hydrogenation of MEA-imine to (*S*)-NAA marks the key step in the synthesis of (*S*)-Metolachlor developed by Ciba-Geigy. Starting from MEA-imine, what is derived from the reaction of methoxyacetone and 2-methyl-6-ethyl aniline (MEA), the (*S*)-NAA can be attained in

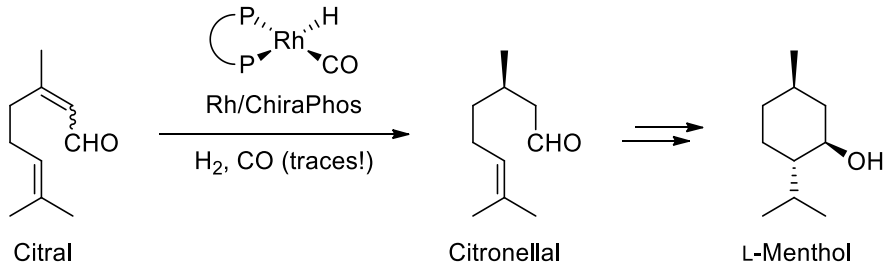
[i] In the case of a C_2-symmetric ligand (e.g (*R*,*R*)-Me-DuPhos), both possibilities for the coordination of the ligand result in the same geometry of the catalyst.
[ii] The Halpern-mechanism is also called "major-minor concept".
[iii] For both enantiomers of Metolachlor it exists also two atropisomers resulted by a chiral axis. Both atropisomers of (*S*)-Metolachlor exhibit the same biological activity, while the other ones (for (*R*)-Metolachlor) are inactive.

79 %ee with almost full conversion. The target benchmark[i] was significantly exceeded through a TOF >400'000 h^{-1} and a TON >2'000'000.



Scheme 3. Stereoselective hydrogenation of MEA-imine to (*S*)-NAA and subsequent transformation into (*S*)-Metolachlor.

Since 2012, the hydrogenation of citral to achieve citronellal has superseded the Metolachlor-process as the largest industrial process with more than 20'000 t/a. This is the key step for the synthesis of L-menthol at BASF (Scheme 4). Remarkably, a typical "hydroformylation catalyst" is used, which is prepared from a reaction of the precursor with CO. Also in the subsequent hydrogenation, a small concentration of CO in the hydrogen stream has to be maintained.[11]



Scheme 4. Enantioselective hydrogenation of citral to Citronellal and final conversion to L-Menthol.

A very recent example, which is of particular economic and medicinal importance, is the diastereoselective hydrogenation of Artemisinic acid. The substrate is produced with the assistance of genetically modified yeast. Subsequent hydrogenation with a diphenyl-diphosphine-based ruthenium catalyst gives the product in high diastereoselectivity that is then converted to Artemisinin.[ii]

[i] The main goal for the synthesis of (*S*)-Metolachlor was to reach TOF's >10'000 h^{-1}, TON's >50'000 and ee's ≥80 %.

[ii] The development of the technical process was financed by the Bill-and-Melinda-Gates-foundation and shall contribute to the reconvalescence of millions of humans suffer from Malaria in Africa.

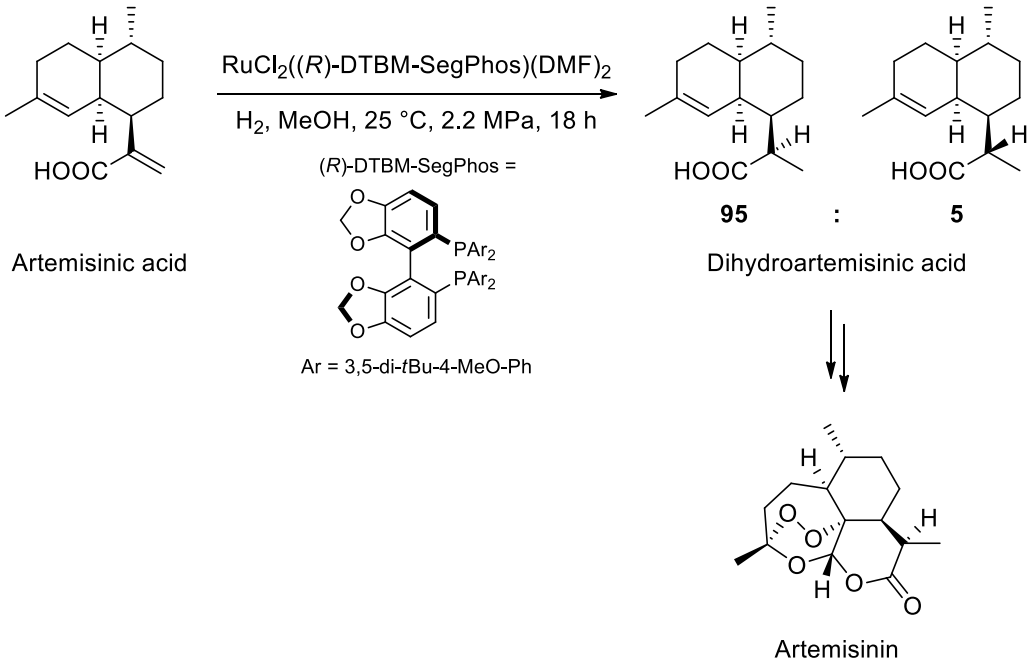


Figure 4. Synthesis of Artemisinin: the diastereoselective hydrogenation of Artemisinic acid to yield Dihydroartemisinic acid represents the key step.

Also 1,1-disubstituted olefins, considered in this thesis, are used as starting material for the production of enantiomerically pure hydrogenation products, such as L-DOPA[12] (Figure 5). The syntheses of (*S*)-Naproxen and (*S*)-Ibuprofen (Figure 5), which could be also realized by asymmetric hydrogenation, do not play an important role on an industrial-scale due to the poor accessibility of the substrates.

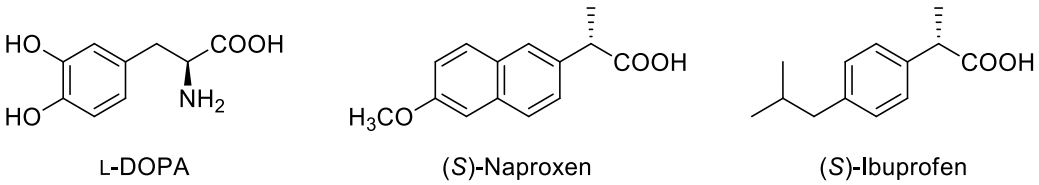
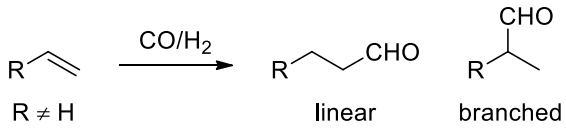


Figure 5. L-DOPA, (*S*)-Naproxen and (*S*)-Ibuprofen derived from 1,1-disubstituted olefins as precursors.

2.2 Hydroformylation

The hydroformylation[i] is formally a reaction of an alkene with hydrogen (H_2) and carbon monoxide (CO) under formation of an aldehyde (Scheme 5).



Scheme 5. Hydroformylation of olefins.

[i] The hydroformylation is also known as "oxo synthesis".

This reaction was discovered by Roelen at Ruhrchemie in 1938[13] in the framework of investigation on the Fischer-Tropsch-synthesis and is nowadays one of the biggest and most important reactions in homogeneous catalysis worldwide with ca. 10.8 Mt/a (2002).[14]
Its products (aldehydes, alcohols, esters) are applied in many fields of daily life, especially as detergents and surfactants, as plasticizers in the polymer chemistry or as cosmetics (Figure 6).[15]

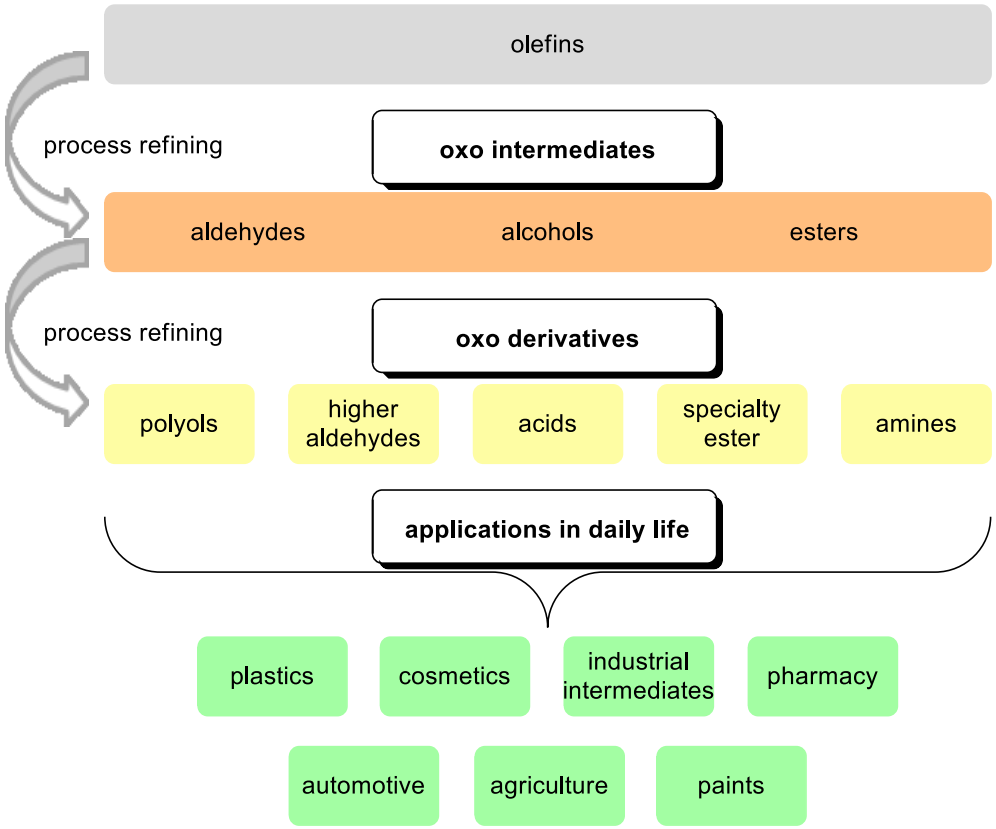
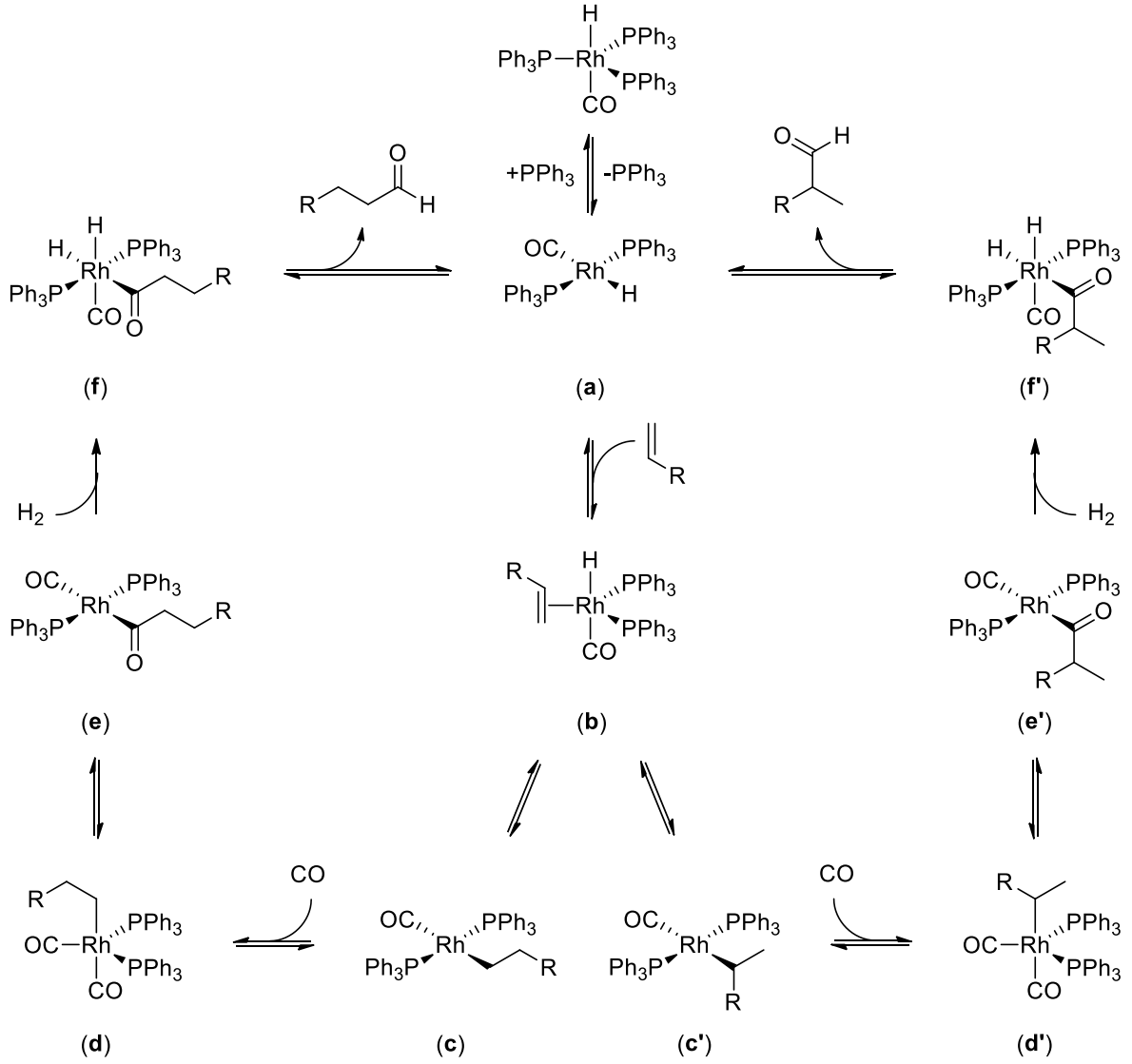


Figure 6. Hydroformylation products and their application.

2.2.1 Principles and generals

Contrary to the hydrogenation, in hydroformylation the double bond is not attacked by two (equal) atoms (H), but is formally linked to a hydrogen atom and a formyl group. Due to this fact, two regioisomers can result for a terminal olefin with a carbon chain number longer than two (when isomerization is omitted): linear aldehydes, whereby the carbonyl group is linked to the terminal position (*n*-aldehydes), or branched (*iso*-) aldehydes, which result from an attack on the interior side of the double bond. The generally accepted catalysis mechanism was established by Wilkinson and co-workers (Scheme 6, dissociative mechanism).[16]



Scheme 6. Dissociative mechanism for the hydroformylation of a terminal olefin and the formation of regioisomers according to Wilkinson.

Starting from the triganol bipyramidal complex $HRh(PPh_3)_3(CO)$, the quadratic planar hydride-complex $HRh(PPh_3)_2(CO)$ (**a**) is formed by dissociation of one PPh_3-molecule. One coordination side is now vacant to bind the alkene under formation of a π-complex (**b**). The σ-complex is formed by insertion. At this point, two routes are possible depending on what carbon atom the metal-alkyl bond is established. Without isomerization the *n*-alkyl-metal-complex leads in the last step to the terminal aldehyde, whereas the branched intermediate gives rise to the *iso*-aldehyde (**c** or **c'**). When a further CO-molecule is taken up, the trigonal bipyramidal complex is formed (**d** or **d'**). Insertion of CO results in the formation of the quadratic planar $Rh(PPh_3)_2(CO)$(acyl)-complex (carbonylation to **e** or **e'**). Oxidative addition of hydrogen gives complex **f** and **f'**, respectively. On hydrogenolysis, the linear or the branched aldehyde are liberated and the unsaturated $HRh(PPh_3)_2(CO)$-complex (**a**) is regenerated that closes the catalytic cycle.

What regioisomer is mostly favored depends on many factors, such as nature of the ancillary ligand, reaction conditions and structure of the substrate.

One can assume that bulky ligands as well as an increased concentration of ligand lead to an enhanced amount of linear aldehyde. Steric congestion around the rhodium results in an overfull complex that consequently coordinates to the less hindered side of the olefin. Usually, the formyl group is not linked

to a tertiary C-atom, which is expressed in Keulemans' rule.[17] However, this empirical rule could be disproved for a few examples.[18]

As already pointed out, organic ligands have a great influence on the success of the reaction. They can determine reactivity, regioselectivity as well as stereoselectivity and affect the amount of side products (chemoselectivity), too. Most important parameters are their sterically demanding and electronic properties. Tolman developed a model to measure the steric demand that enables a comparison of several ligands with regard to their size. This concept of a *cone angle* (θ) is based on the measurement of the angle, what emerges between the arms of the axis from metal to the outer edge of one substituent, starting from the metal as apex.[19] Originally, the distance between the metal center and the coordinating atom, that bears all substituents, is defined as 2.28 Å (Figure 7).

The steric demand of bidentate ligands can be described with the natural *bite angle* (β_n), which was suggested by Casey and Whiteker.[20] Hereby, the angle, spanned between both donor atoms and the metal, is measured while the chelating ligand coordinates (Figure 7). The concept was proved in detail with xanthene-based diphosphines (XantPhos-type ligands).[21]

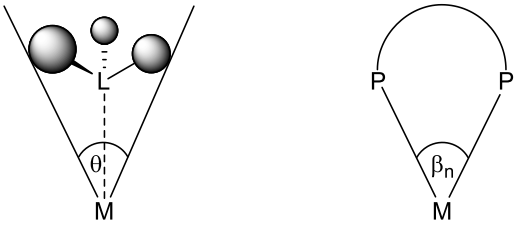


Figure 7. Tolman's *cone angle* (θ) and the natural *bite angle* (β_n).

In Figure 8 are given some *bite angles* of characteristic bidentate ligands.[22]

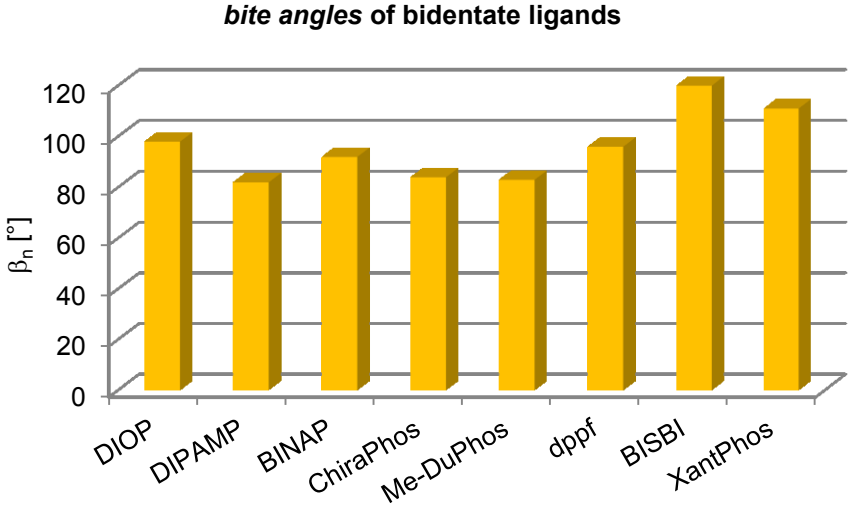
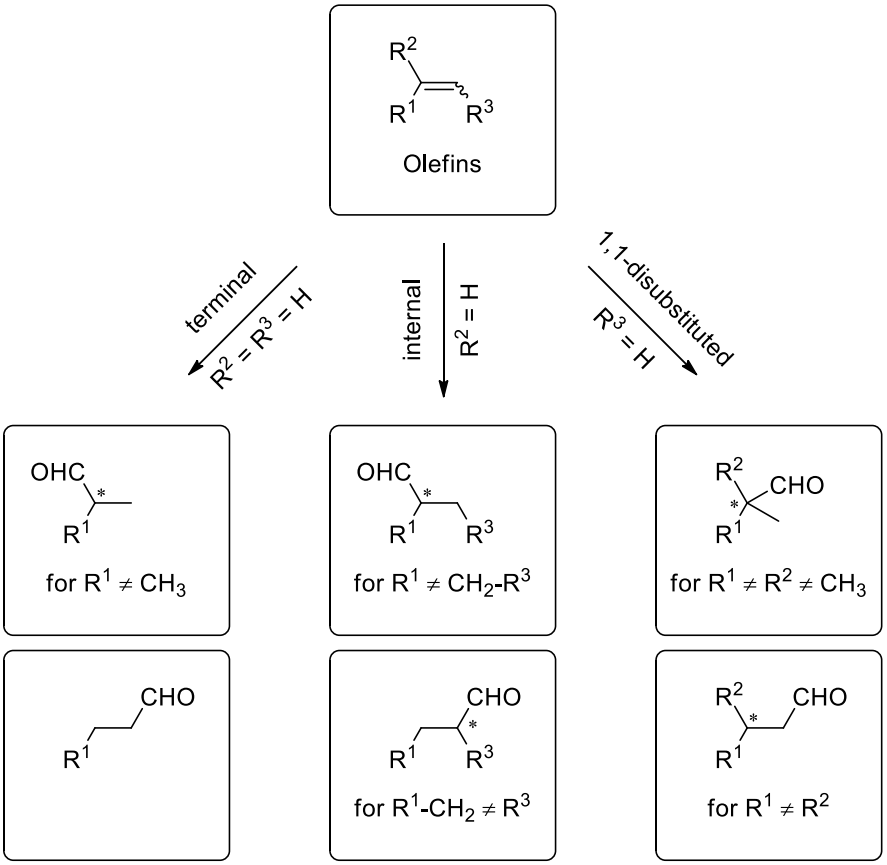


Figure 8. *Bite angles* of selected bidentate ligands.

The *bite angle* has an decisive influence on the regioselectivity.[23] The larger it is, the more increases the possibility that the ligand adopts **ee**-coordination (equatorial-equatorial), whereas **ea**-coordination (equatorial-apical) is especially favored when the ligand has only a small *bite angle*.[22a]

When chiral ligands are used, asymmetric hydroformylation (AHF) can be achieved.[24] The goal is to get predominantly a single enantiomer. Depending on the alkenes (monosubstituted, 1,2-, or 1,1-disubstituted) submitted to the reaction, different chiral aldehydes can be obtained. For terminal

olefins only the branched product is chiral, whereas the linear aldehyde is achiral. Internal and also 1,1-disubstituted olefins can give chiral products for both regioisomers (Scheme 7).



Scheme 7. (Asymmetric) hydroformylation of terminal, internal and 1,1-disubstituted olefins and their hydroformylation products.

2.2.2 Asymmetric hydroformylation

During the last three decades, asymmetric hydroformylation[18a,25] has been developed as an elegant process[26] to convert prochiral olefins into enantiomerically pure aldehydes in one step. They serve as a lucrative starting material for a large number of interesting compounds. Despite of great investigations and a huge number of chiral phosphorus ligands,[25a,b] that have been established in rhodium-catalyzed asymmetric hydroformylation, the range of potential substrates is limited to monosubstituted[25a,27] and 1,2-disubstituted[28] olefins.

2.2.2.1 Potential industrial application of asymmetric hydroformylation

Today, asymmetric hydroformylation does not play a considerable role in industry. Main reasons are the low productivity of the catalysts and, in several cases, the poor accessibility of the substrates. Nevertheless, some approaches, developed on small-scale, desire attention. For example, (*R*)-Flurbiprofen, (*S*)-Ketoprofen and (*S*)-Tiaprofenic acid (Figure 9) could be synthesized starting from the relevant vinyl aromatics by hydroformylation and final oxidation.[29] This method could represent an alternative compared to the enantioselective hydrogenation (see above), because starting vinyl compounds can be synthesized with much less efforts in comparison to relevant 2-substituted acrylates. In the same manner, the preparation of enantiopure Naproxen and Ibuprofen has been taken into consideration.

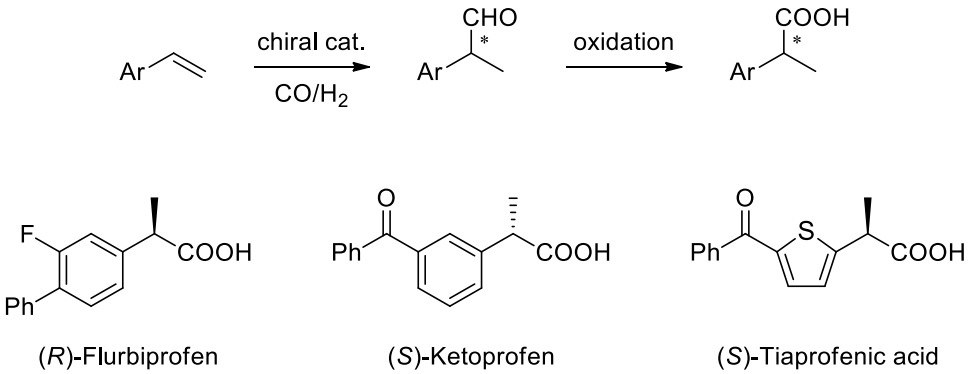
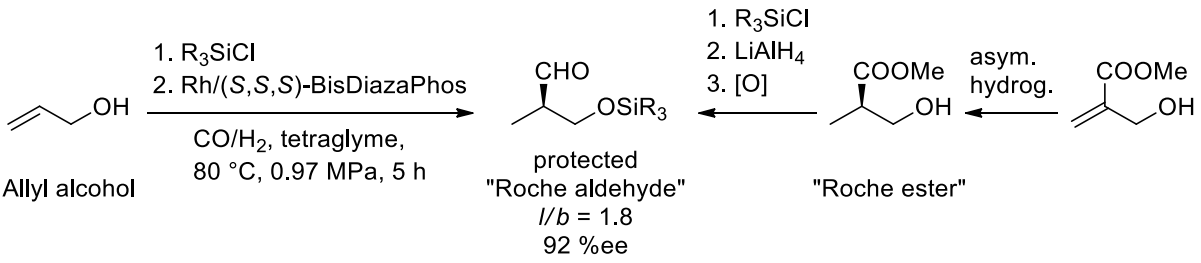


Figure 9. Examples for the application of enantioselective hydroformylation: (*R*)-Flurbiprofen, (*S*)-Ketoprofen and (*S*)-Tiaprofenic acid.

The competition for the optimal asymmetric access can also be illustrated with the so-called "Roche aldehyde" in hand. Usually, this compound is prepared by asymmetric hydrogenation and subsequent two step conversion of the formed "Roche ester".[30] An approach, which is based on the asymmetric hydroformylation, should be shorter.[i] Indeed, with a Rh catalyst, based on (*S,S,S*)-BisDiazaPhos, the branched aldehyde was achieved, starting from the corresponding *O*-silylether, in excellent enantioselectivities (up to 97 %). In 2012, this synthesis route was up-scaled[31] (Scheme 8).

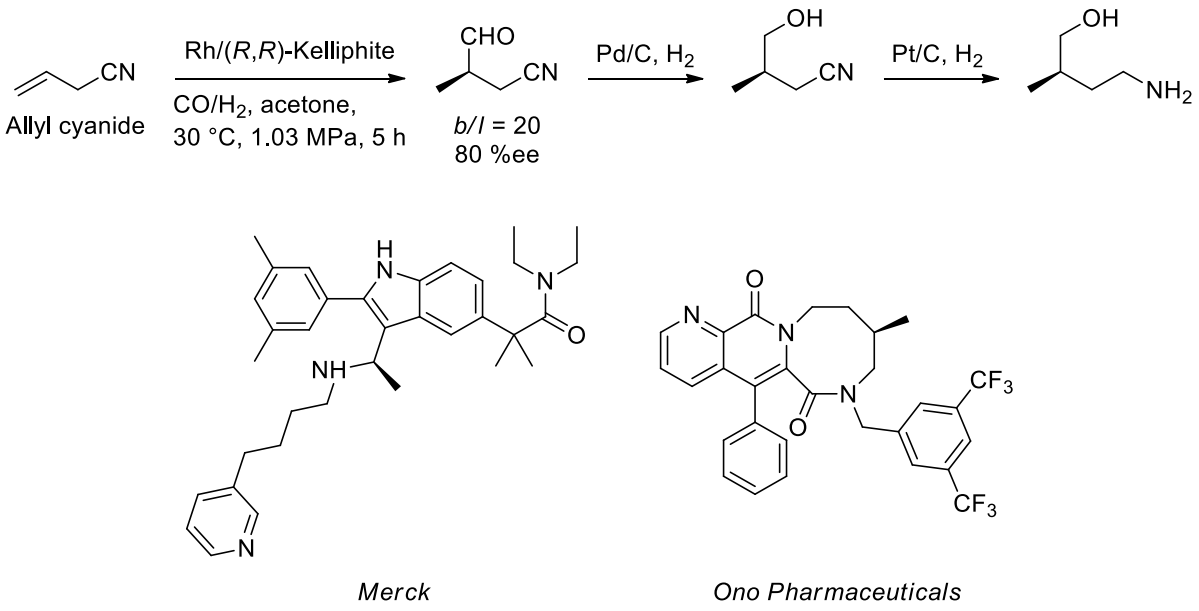


Scheme 8. An alternative synthetic strategy to the "Roche aldehyde" by asymmetric hydroformylation.

Also, the asymmetric hydroformylation of structurally related allyl cyanide gives access to some important pharmaceuticals developed by Merck and Ono Pharmaceuticals. Researchers from Dowpharma, using a Rh/(*R,R*)-Kelliphite catalyst under mild conditions, were able to achieve a *b/l* ratio of 20/1 and an enantioselectivity of 80 % for the desired chiral aldehyde. (Scheme 9).[27a] Thus, prior results, obtained from Rh/(*R,S*)-BINAPHOS, could be improved enormously.[ii] Up-scaling to ca. 1 mol-scale of substrate was possible after optimization of the reaction conditions.

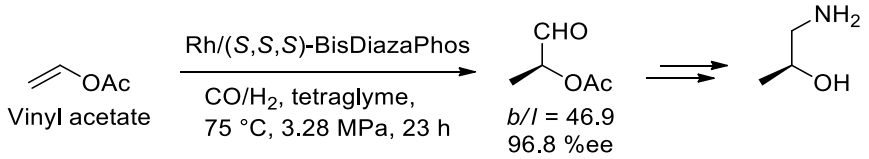
[i] A price of \$0.04/g for allyl alcohol compared to that of the "Roche ester" (\$14/g) emphasizes the importance of asymmetric hydroformylation to yield the "Roche aldehyde".[31]

[ii] The rhodium-catalyzed hydroformylation of allyl cyanide gave only a *b/l* ratio of 72/28 and 66 %ee with (*R,S*)-BINAPHOS as ligand.[32]



Scheme 9. Asymmetric hydroformylation of allyl cyanide and subsequent steps to pharmaceutically interesting compounds.

Asymmetric hydroformylation of vinyl acetate is another example of potential application in fine chemistry. The reaction on a 150-180 g-scale was performed with a rhodium catalyst based on (*S,S,S*)-BisDiazaPhos and proceeds with >90 % conversion and a TOF of 19'400 h^{-1} (TON = 99'962).[33] Starting from the chiral aldehyde, obtained with 96.8 %ee, subsequent transformations, e.g. to chiral 1,2-amino alcohols, were possible (Scheme 10).



Scheme 10. Asymmetric hydroformylation of vinyl acetate and subsequent transformation.

2.2.2.2 Enantioselective hydroformylation of 1,1-disubstituted olefins

Up to now, the enantioselective hydroformylation of 1,1-disubstituted substrates was much less investigated.[18b-d,24,28a,34] First work was done by Consiglio and Morandini in 1985.[34a] Hydroformylation of α-methyl styrene using both, $PtCl_2/SnCl_2$ and different rhodium catalysts, led either with (*S,S*)-ChiraPhos or (*R,R*)-DIOP to poor ee-values of maximum 21 %. Although extraordinarily long reaction times (up to 70 h) were applied, only low to moderate conversions were noted. In 2004, Takahashi obtained 3-phenylbutanal as product deriving from α-methyl styrene with $[(Rh(cod)_2(OAc)]_2$ and a self-prepared diphosphite ligand in 46.2 %ee, what is highest up to now.[34b] However, the conversion was quite poor (15 %).

In 1987, Stille and co-workers described the reaction of methyl methacrylate with syngas.[34c] A [(–)-BPPM]$PtCl_2/SnCl_2$ catalyst was employed,[35] which required strongly elevated syngas pressures (18.3 MPa) and also long reaction times (50 h) to provide the linear aldehyde with low to moderate enantioselectivities, but little conversions. Both parameters showed opposing tendencies: increasing the conversion by changing the ratio of partial pressures of hydrogen to carbon monoxide lowered the enantioselectivity and vice versa. Also a few (hydrogenation) by-products were observed, but the selectivity still remained superb.

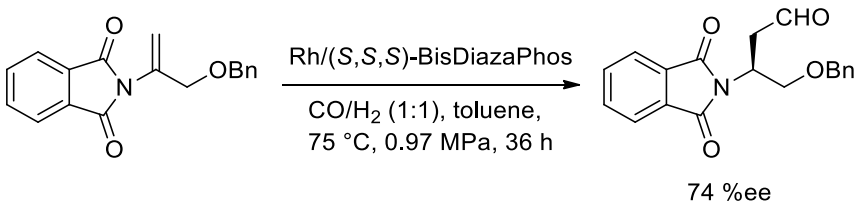
In the same year, Kollár *et al.* expanded the scope for the asymmetric hydroformylation of 1,1-disubstituted olefins to α-alkyl acrylates as well as itaconates.[34d] However, the reaction was still performed with a $PtCl_2/SnCl_2$ catalyst using chiral DIOP as ligand that likewise required high syngas pressures (8 MPa) to be stable. Lowering the temperature from 100 °C to 50 °C resulted in much better enantioselectivities (up to 82 %), but enormously affected the yield of the chiral aldehyde. Furthermore, under these conditions, also competitive and undesirable hydrogenation became more significant.

In 1988, Kollár published the results of the asymmetric hydroformylation of different substrates, including α-methyl styrene, methyl methacrylate and methyl itaconate, based on a platinum-tin catalyst using BDPP as ligand. Next to significant amounts of hydrogenation products, low yields of the desired aldehydes were obtained with mediocre enantioselectivities.[34e]

In 1990, this working group published some results for the asymmetric hydroformylation of a few acrylates and acrylamides while testing some Pt, Pd and Rh catalysts. However, medium success with respect to enantioselectivity was achieved.[34f]

In the same year, Gladiali reported the first rhodium-catalyzed asymmetric hydroformylation of (2-acetamidomethyl)acrylate, but surprisingly, only the branched aldehyde was formed (against Keulemans' rule) with a good yield (up to 90 %) and enantioselectivity of about 50 %. Improved ee's could be realized with a lower temperature (30 °C), what required a much longer reaction time and was accompanied with a loss of reactivity.[18a-c]

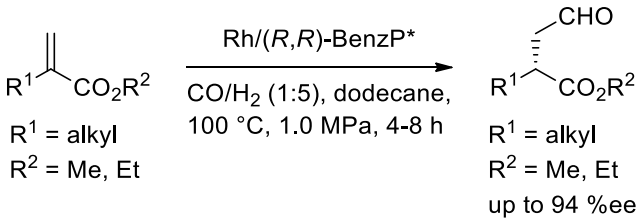
The great breakthrough in the rhodium-catalyzed hydroformylation of 1,1-disubstituted olefins was realized by Landis and co-workers in 2010.[28a] They established the hydroformylation of a *N*-(1-alkyl)vinyl phthalimide as a novel and efficient route to a chiral β^3-aminoaldehyde. The catalyst was prepared from $Rh(acac)(CO)_2$ with a self-prepared (*S*,*S*,*S*)-BisDiazaPhos as ligand. The rhodium catalyst allowed a mild reaction regime with low syngas pressure (1 MPa) and moderate temperature, what led to high selectivity to the linear chiral aldehyde in good enantioselectivity (up to 74 %). Next to the aldehyde, significant amounts of the isomerization product were detected (Scheme 11).



Scheme 11. Asymmetric hydroformylation of a *N*-(1-alkyl)vinyl phthalimide.

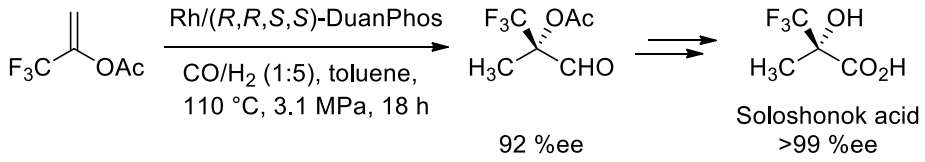
Wang and Buchwald showed that the regioselectivity is dependent on the nature of the substrate. However, high enantioselectivities could be reached in both cases.[18d,24a]

A wide scope of α-alkyl acrylates were submitted to the rhodium-catalyzed reaction with (*R*,*R*)-BenzP* and (*R*,*R*)-QuinoxP* as ligands.[24a,34g] Primarily, they achieved only low yields of aldehyde with a large amount of hydrogenated substrate, what they could counteract with a higher ratio of the hydrogen to carbon monoxide partial pressure without losing any enantioselectivity. With this reaction system ee-values up to 94 % were reached that was highest until then (Scheme 12).



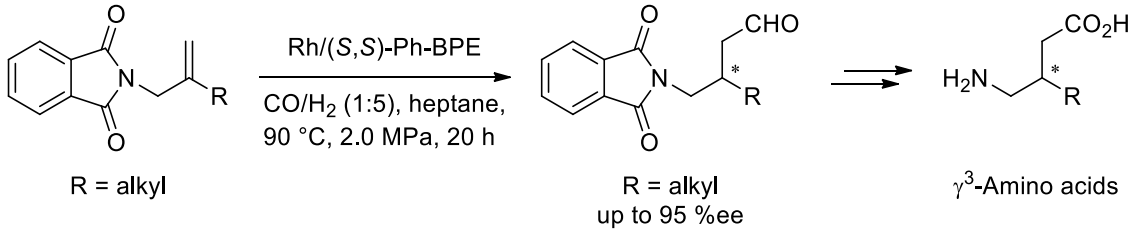
Scheme 12. Asymmetric hydroformylation of α-alkyl acrylates.

Furthermore, Wang and Buchwald found a highly enantioselective way for the synthesis of optically pure 2-trifluoromethyllactic acid[i] (TFMLA) based on enantioselective hydroformylation (Scheme 13).[18d]



Scheme 13. Asymmetric hydroformylation to produce Soloshonok acid.

As main product the internal aldehyde was found against Keulemans' rule. Applying both commercially available *P*-chiral ligands (*R*,*R*,*S*,*S*)-DuanPhos and (*R*,*R*)-QuinoxP* they could reach ee's up to 92 %. For the lactic acid derivative, that can be utilized for the production of the so-called Soloshonok acid, it was possible to raise the enantiomeric excess to >99 % by crystallization.
Quite recently, Zhang and co-workers presented an elegant catalytic route to γ^3-amino acids based on the rhodium-catalyzed asymmetric hydroformylation of prochiral allyl phthalimides (Scheme 14).[24b]



Scheme 14. Asymmetric hydroformylation of prochiral allyl phthalimides.

While testing commercially available ligands they found (*S*,*S*)-Ph-BPE as the most appropriate: excellent ee-values up to 95 % were achieved, albeit a relative high amount of rhodium (2 mol%) and a high loading with ligand (10 mol%) were used. However, moderate conversions and significant hydrogenation rates still remained a problem.
Not least, this substrate class is extremely difficult to be converted enantioselectively. Controlling the chemo-, regio- and stereoselectivity, it is still a great challenge to be solved.

2.3 Ligands

2.3.1 Phosphines

Chiral phosphines were the first ligands introduced for the asymmetric hydrogenation by the pioneers Horner and Knowles.[36] Through the years, more and more phosphine ligands with either a

[i] Soloshonok acid is a nucleophilic glycine equivalent for the synthesis of α-amino acids.

stereogenic phosphorus atom[37] or stereogenic centers located at their backbone[38] have been applied for the asymmetric hydrogenation. By using other forms of chirality, deriving form e.g. a chiral axis,[39] a wide scope of ligands could be prepared. This type of ligand is easily tuneable with respect to the electronic properties and steric demand.[40] Since the early 1990s, phospholane ligands[41] have been of interest to the asymmetric hydrogenation. By modification of the phospholane rings by polar groups,[i] an opportunity was created to improve their solubility in the solvent.[38a,42]
Quite recently, ligands like diphospholane (*S*,*S*,*S*)-BisDiazaPhos[43] and also *P*-chiral (*R*,*R*)-QuinoxP*[44] and (*R*,*R*)-BenzP*[45] (Figure 10) were efficiently used in asymmetric hydroformylation.

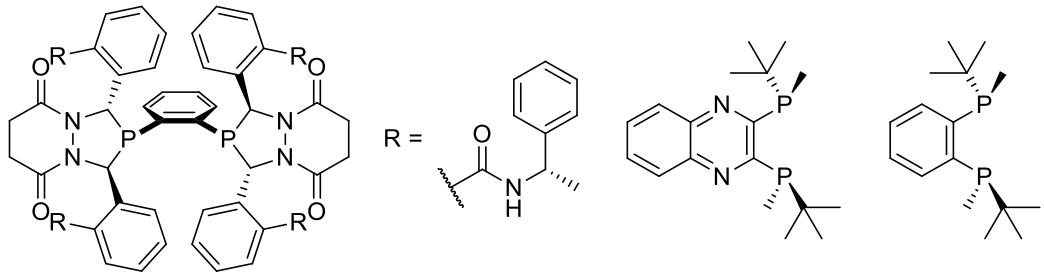


Figure 10. Ligands for asymmetric hydroformylation: (*S*,*S*,*S*)-BisDiazaPhos, (*R*,*R*)-QuinoxP* and (*R*,*R*)-BenzP*.

2.3.2 Phosphites

As generally known, in contrast to phosphines, organophosphite ligands are weak σ-donors, but strong π-acceptors. This property facilitates the dissociation of CO from a metal center and the subsequent insertion into the Rh-acyl bond. As a consequence, the rate of hydroformylation is enhanced.[25c]
Their relatively simple synthesis from alcohols and their stability toward oxidation make them valuable for an application. However, this type of ligands is usually more prone to hydrolysis. Noteworthy, the number of commercially available and successfully applied chiral diphosphite ligands[25a] is limited up to now.
In 1992, Babin and Whiteker from Union Carbide reported a chiral diphosphite named (*R*,*R*)-Chiraphite (Figure 11).[46] It is prepared from (2*R*,4*R*)-pentane-2,4-diol and bears bulky achiral biphenols at the phosphorus atoms. By varying the biphenol substituents, bearing different sterically demanding and electronical groups in *ortho*- and *para*-position at the *P*-atoms, the ligand library could be easily expanded. (*R*,*R*)-Chiraphite-based rhodium-complexes manage the enantioselective hydroformylation of various alkenes with ee's up to 90 %.[46]
When the chirality was shifted from the backbone to the substituent at the phosphorus, further classes of chiral diphosphites became available. (*S*,*S*)-Kelliphite (Figure 11) with an achiral biphenol as backbone and bulky biphenols at the phosphorus atoms, deriving from chiral BIPHEN-H_2, was first mentioned by Whiteker in 2004.[27a] Compared to its relatives it was most efficient with respect to regio- and enantioselectivities in asymmetric hydroformylation of allyl cyanide[27a] as well as vinyl acetate.[47]

[i] Chiral BasPhos and RoPhos (Börner) are two examples of ligands, which show an increased solubility in water in comparison to chiral Me-Duphos due to additional polar groups at the phospholane units.

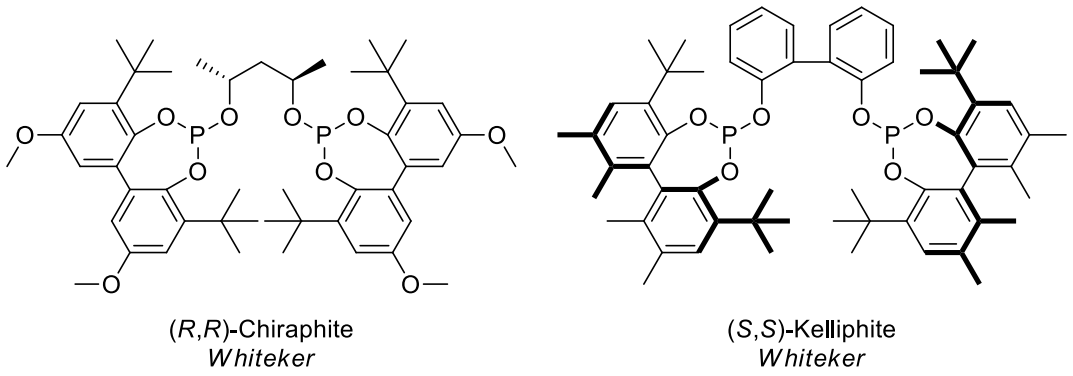


Figure 11. Commercially available chiral diphosphites: (*R*,*R*)-Chiraphite and (*S*,*S*)-Kelliphite.

2.3.3 Phosphine-phosphites and -phosphoramidites

A breakthrough in asymmetric hydroformylation was achieved by Takaya and Nozaki by introducing BINAPHOS in 1991 (Figure 12), a chiral phosphine-phosphite with binaphthyl backbone.[48] This ligand shows excellent ee's for a wide range of substrates[28b,48-49] and combines high enantioselectivity, as known from phosphines, with the superior activity, a property of the phosphite moiety.[22a]

Zhang and co-workers published the phosphine-phosphoramidite YanPhos (Figure 12) derived from BINAPHOS, where one oxygen atom was replaced by an EtN-fragment.[50] It even shows better stereodifferentiation for many substrates. Unfortunately, regioselectivities were as moderate as for hydroformylation of both, styrene and vinyl acetate, executed by BINAPHOS.

The recently introduced (S_{ax},*S*,*S*)-BobPhos[i] by Clarke is a non-symmetric phosphine-phosphite ligand that possesses a chiral axis as well chiral phospholane unit. With this ligand high enantioselectivities up to 93 % could be attained for the branched aldehyde starting from different terminal alkenes[51] as well as an unusually high regioselectivity in the enantioselective hydroformylation of vinyl arenes (*b*/*l* = 79, 92 %ee).[52]

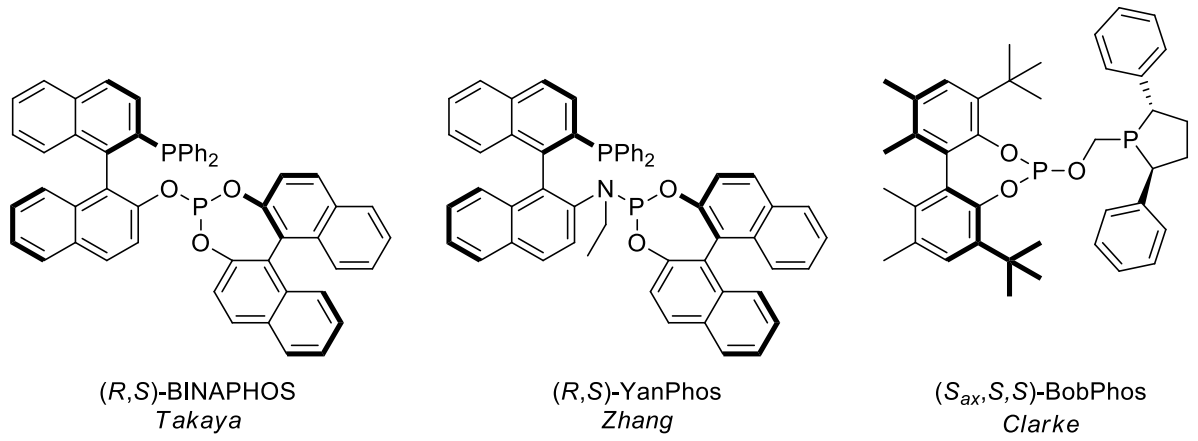
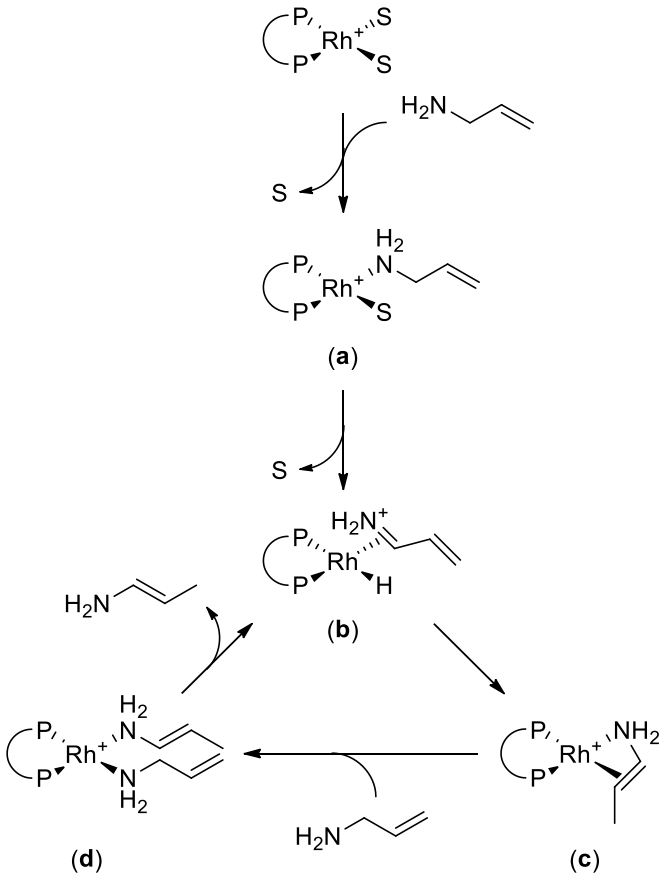


Figure 12. Chiral phosphine-phosphite and -phosphoramidite ligands: (*R*,*S*)-BINAPHOS, (*R*,*S*)-YanPhos and (S_{ax},*S*,*S*)-BobPhos.

[i] The name "BobPhos" is derived from "**B**est **o**f **b**oth of phosphorus ligands" and means a combination of both advantages coming from the BIPHEN-H_2-scaffold of Kelliphite and the phospholane unit of Ph-BPE. Since Rh/Kelliphite is high active under mild conditions even for internal aldehydes, Rh/Ph-BPE displays a robust catalyst precursor that gives high enantioselectivies for terminal alkenes.

2.4 Isomerization

Isomerization of olefins frequently accompanies hydrogenation and hydroformylation. Functional groups can support the migration of an olefin. Hereby, three principal mechanisms can be differentiated: the metal hydride addition-elimination mechanism (alkyl mechanism),[53] reaction via a π-allyl metal hydride intermediate (allyl mechanism)[54] and isomerization of allylamines or allyl alcohols. For the topic, considered herein, the latter is of greater relevance and shown in Scheme 15.[55] It can also be used in an asymmetric version.[56]



Scheme 15. Mechanism of the rhodium-catalyzed isomerization with allylamine.

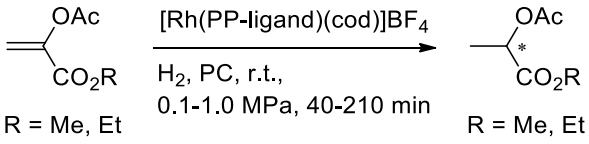
Starting from the cationic quadratic planar complex Rh(PP-ligand)$(S)_2$, one solvent molecule S is replaced by the amine. In a consequence, the σ-complex (**a**) is formed. By dissociation of the second solvent ligand β-hydride elimination occurs and one hydride is transferred to rhodium. As a result, the π-complex (**b**) is generated. Due to the conjugation of the double bond, facile rearrangement happens and the hydride is retransferred to the coordinated amine. Both, the nitrogen and the olefin coordinate simultaneously to the rhodium (**c**). When a further allylamine binds to the metal (**d**), the enamine is released and the π-complex (**b**) is formed back by β-hydride elimination to restart the catalytic cycle.

3 Results and discussion

3.1 Hydrogenation

3.1.1 Preparation of lactic acid derivatives

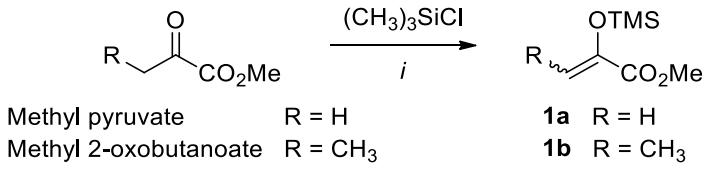
For the last years, the demand of enantiomerically pure lactic acid has increased enormously. Its importance as a building block for the synthesis of biodegradable chiral polylactic acids (PLAs) can be explained by a range of applications similar to the one of polyethylene terephthalate (PET).[57] Nowadays, enantiopure lactic acid is generally derived from sugar feedstocks by fermentation. Undoubtedly, chemical synthesis and particularly asymmetric hydrogenation present an interesting alternative to this route, especially in terms of efficiency and sustainability. The latter has found a broad range of application in industry as environmentally friendly technology in the synthesis of chiral compounds.[9a,58] Homogeneous catalysts, such as rhodium, ruthenium and iridium, based on chiral phosphorus ligands play a crucial role for this task.[59]
Enantiopure lactic acid and its derivatives have been synthesized via asymmetric hydrogenation starting from corresponding pyruvates.[60] Burk recently published the results of a highly enantioselective hydrogenation of the unsaturated lactate precursor α-acetoxy ethyl acrylate (up to >99 %ee using DuPhos as ligand).[61] Schäffner *et al.* were able to extend the ligand library to a wide range of structurally related compounds and reached ee-values up to 98 %.[62] With Rh catalysts based on ligands of the cat*AS*ium®M series, full conversions were achieved in propylene carbonate (PC) as economically benign solvent (Scheme 16).



Scheme 16. Asymmetric hydrogenation of lactic acid precursors.

3.1.1.1 Synthesis of 2-trimethylsilyloxy methyl acrylate and crotonate

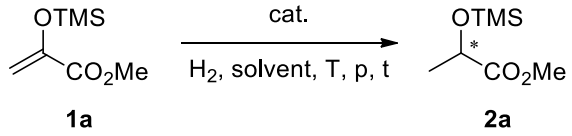
Prochiral 2-trimethylsilyloxy methyl acrylate was prepared from readily available methyl pyruvate and chlorotrimethylsilane in the presence of triethylamine according to the procedure of Bäckvall.[63] The silicon attacks the oxygen and, consequently, the double bond rearranges under formation of the corresponding TMS-protected compound **1a**. After filtration from ammonium chloride and aqueous work-up, the desired product **1a** could be obtained from Kugelrohr distillation as colorless oil in 99 % yield.
Starting from methyl 2-oxobutanoate, the homologue *O*-trimethylsilyl-protected olefin **1b** is yielded in 94 % after Kugelrohr distillation as colorless oil (Scheme 17). Both compounds tend to polymerize, but can be stored at 5 °C for a few days.



Scheme 17. Preparation of prochiral 2-trimethylsilyloxy methyl acrylate **1a** and 2-trimethylsilyloxy methyl crotonate **1b**: (*i*) 1.6 eq Et_3N, DCM, r.t., 18 h.

3.1.1.2 Asymmetric hydrogenation of 2-trimethylsilyloxy methyl acrylate and crotonate

2-Trimethylsilyloxy methyl acrylate **1a** served as a test substrate for the asymmetric hydrogenation using a variety of catalysts and conditions (Scheme 18). The absolute configuration of the hydrogenation product was compared to enantiomerically pure *O*-TMS-protected methyl lactates prepared by an alternative pathway[i] (Table 1).



Scheme 18. Hydrogenation of prochiral 2-trimethylsilyloxy methyl acrylate **1a**.

Table 1. Initial trials of the asymmetric hydrogenation of prochiral **1a** with [Rh(PP-ligand)(cod)]BF_4.[a]

Entry	Ligand	ee[b] [%]
1	(*R*,*R*)-DIPAMP	rac
2	(*R*)-BINAP	rac
3	(*S*,*S*)-Me-BPE	n.d.[c]
4	(*S*,*S*)-Me-DuPhos	1 (*S*)
5	cat*AS*ium®MQF(*R*)	6 (*R*)
6	(*R*)-MeO-BIPHEP	2 (*R*)
7	1,1'-Bis[(2*R*,5*R*)-2,5-di-isopropylphospholano]ferrocene	3 (*R*)
8	(*R*,*S*)-dppf'bp	1 (*S*)

[a] 1.0 mmol of **1a**, [Rh(PP-ligand)(cod)]BF_4 10.0 µmol, H_2, 4 mL of THF, 40 °C, 1.5 MPa, S/Rh = 100, 20 h.
[b] Full conversion was observed in all cases, determined by ^{1}H NMR spectroscopy; ee-values were determined by GC analysis; absolute configurations were compared to synthesized enantiomerically pure *O*-silylated methyl lactates.
[c] No hydrogenation product could be detected by ^{1}H NMR spectroscopy due to decomposition.

The asymmetric hydrogenation of **1a** was performed in THF at a temperature of 40 °C and under a hydrogen atmosphere of 1.5 MPa. In all cases, full conversion could be detected via NMR. However, lactates, which were achieved from the hydrogenation with rhodium catalysts, based on ligands like (*R*,*R*)-DIPAMP or (*R*)-BINAP, were obtained as racemates (entries 1,2). Rh/Me-DuPhos, as a preferred catalyst for the enantioselective hydrogenation of structurally related α-acetoxy acrylates,[61] was also unable to induce any significant stereoselectivity (entry 4). Ligands, that have different electronic and steric properties, such as cat*AS*ium®MQF(*R*) (entry 5) and (*R*)-MeO-BIPHEP (entry 6), respectively, do not crucially affect the stereodiferrentiation. Subsequently, we switched to ruthenium and iridium as metals (Table 2).

[i] Enantiomerically pure (*S*)- and (*R*)-*O*-TMS-protected methyl lactate, respectively, was prepared by reaction of its corresponding chiral lactate with TMSCl in the presence of Et_3N.

Table 2. Initial trials of the asymmetric hydrogenation of **1a** with ruthenium and iridium.[a]

Entry	Precatalyst	*T* [°C]	*p* [MPa]	Yield[b] [%]	ee[c] [%]
1	(*R*)-BINAP-$RuCl_2$	40	1.5	6	31 (*S*)
2	[Ru(*p*-cymene)((*R*)-C_3-TunePhos)Cl]Cl	40	1.5	48	56 (*S*)
3	Crabtree's catalyst	40	1.5	57	1 (*S*)
4	(*R*)-BINAP-$RuCl_2$	50	5.0	98	47 (*S*)
5	[Ru(*p*-cymene)((*R*)-C_3-TunePhos)Cl]Cl	50	5.0	>99	53 (*S*)
6	Crabtree's catalyst	50	5.0	54	rac
7[d]	(*R*)-BINAP-$RuCl_2$	60	10.0	>99	52
8[e]	(*R*)-BINAP-$RuCl_2$	60	10.0	>99	49
9[d]	[Ru(*p*-cymene)((*R*)-C_3-TunePhos)Cl]Cl	60	10.0	>99	52
10[e]	[Ru(*p*-cymene)((*R*)-C_3-TunePhos)Cl]Cl	60	10.0	>99	45

[a] 1.0 mmol of **1a**, precatalyst 10.0 µmol, H_2, 4 mL of THF, *T*, *p*, S/Rh = 100, 20 h.
[b] Yields were determined by ^{1}H NMR spectroscopy.
[c] Ee-values were determined by GC analysis; absolute configurations were compared to synthesized enantiomerically pure *O*-silylated methyl lactates.
[d] Reaction was performed in DCM.
[e] Reaction was performed in toluene.

Starting with ruthenium, (*R*)-BINAP as well as (*R*)-C_3-TunePhos were tested with substrate **1a**. Under the same conditions, the yield of the product was quite low in comparison with that from the rhodium-catalyzed reaction, although promising ee-values of 31 % and 56 %, respectively, were reached.
Encouraged by this result, an attempt to promote the reaction with higher temperature and higher hydrogen pressure was made. The yield of the desired chiral lactate could be improved from 6 % to 98 % with (*R*)-BINAP-$RuCl_2$ as precatalyst, while the enantioselectivity reached 47 % (entry 4). For the reaction with [Ru(*p*-cymene)((*R*)-C_3-TunePhos)Cl]Cl, a higher conversion was detected, too, but the ee-value slightly dropped (entry 5). At both temperatures, almost no effect on the yield and ee-value in the hydrogenation of **1a** could be noted when Crabtree's iridium catalyst was employed (entries 3,6).
Additionally, the reaction was run with both ruthenium catalysts at a higher temperature, higher hydrogen partial pressure and in two solvents. At a temperature of 60 °C and a hydrogen atmosphere of 10 MPa, the enantiomeric excesses were approximately of the same values for both ligands in DCM and toluene, respectively.
The Ru-catalyzed hydrogenation of **1a**, using (*R*)-C_3-TunePhos, was also tested in a range of solvents owning varied polarity (Table 3).

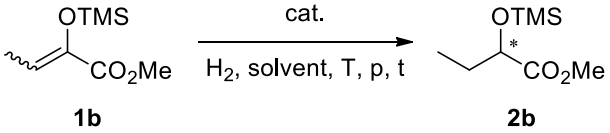
Table 3. Screening of solvents for the asymmetric hydrogenation of **1a** with [Ru(*p*-cymene)((*R*)-C_3-TunePhos)Cl]Cl.[a]

Entry	Solvent	ee[b] [%]
1	THF	53 (*S*)
2	Toluene	55 (*S*)
3	EtOAc	55 (*S*)
4	MeOH	3 (*R*)
5	CF_3CH_2OH	28 (*S*)

[a] 1.0 mmol of **1a**, [Ru(*p*-cymene)((*R*)-C_3-TunePhos)Cl]Cl 10.0 µmol, H_2, 4 mL of solvent, 50 °C, 5.0 MPa, S/Rh = 100, 20 h.
[b] Full conversion was observed in all cases, determined by ^{1}H NMR spectroscopy; ee-values were determined by GC analysis; absolute configurations were compared to synthesized enantiomerically pure *O*-silylated methyl lactates.

Unpolar solvents, such as toluene, do not have a significant influence on the enantioselectivity of the reaction (entry 2), as opposed to THF. When the more polar solvent EtOAc is used, the enantiomeric excess is still at the same level (of 55 %ee). For the effect of solvents it can be concluded that the more polar it is the lower the ee-value of the product is (entries 4,5). Protic solvents do affect the stereoselectivity negatively. Interestingly, for methanol the opposite stereoisomer is favored, even though to only a minor degree. This makes clear that the solvent has an enormous influence on the success of the reaction.

With this result in hands, we screened the most successful precatalysts, [Ru(*p*-cymene)((*R*)-C_3-TunePhos)Cl]Cl as well as (*R*)-BINAP-$RuCl_2$, in the asymmetric hydroformylation of **1b** (Scheme 19, Table 4).



1b **2b**

Scheme 19. Hydrogenation of prochiral 2-trimethylsilyloxy methyl crotonate **1b**.

Table 4. Asymmetric hydrogenation of **1b** with [Ru(*p*-cymene)((*R*)-C_3-TunePhos)Cl]Cl and (*R*)-BINAP-$RuCl_2$ in different solvents.[a]

Entry	Precatalyst	Solvent	Conversion[b] [%]
1	[Ru(*p*-cymene)((*R*)-C_3-TunePhos)Cl]Cl	THF	–
2	[Ru(*p*-cymene)((*R*)-C_3-TunePhos)Cl]Cl	EtOAc	–
3	[Ru(*p*-cymene)((*R*)-C_3-TunePhos)Cl]Cl	Toluene	–
4	[Ru(*p*-cymene)((*R*)-C_3-TunePhos)Cl]Cl	PC	–
5	(*R*)-BINAP-$RuCl_2$	THF	–
6	(*R*)-BINAP-$RuCl_2$	EtOAc	–
7	(*R*)-BINAP-$RuCl_2$	Toluene	–
8	(*R*)-BINAP-$RuCl_2$	PC	–

[a] 0.5 mmol of **1b**, precatalyst 5.0 µmol, H_2, 4 mL of solvent, 50 °C, 8.0 MPa, S/Rh = 100, 20 h.
[b] No conversion was determined in any case by ^{1}H NMR spectroscopy.

To our amazement, both ruthenium catalysts showed no activity in the asymmetric hydrogenation of 2-trimethylsilyloxy methyl crotonate **1b** at 50 °C and 8 MPa hydrogen pressure in all tested solvents. Thus, we moved to other catalytic systems developed from ruthenium precursors, while using THF as solvent (Table 5).

Table 5. Asymmetric hydrogenation of **1b** with different catalysts in THF.[a]

Entry	Precatalyst	Yield[b] [%]	ee[c] [%]
1	[Ru(*p*-cymene)((*R*)-C_3-TunePhos)Cl]Cl	9	6 (–)
2	$RuCl_3$ + (*R*)-4-Tol-BINAP	<5	6 (–)
3	$RuCl_2(C_6H_6)$ + (*R*)-4-Tol-BINAP	8	11 (–)
4	Ru(methylallyl)$_2$(cod) + (*R*)-4-Tol-BINAP	–[d]	n.d.
5	Ru(CF_3COO)$_2$(cod) + (*R*)-4-Tol-BINAP	–[d]	n.d.
6	$RuCl_3$ + (*R*)-MeO-BIPHEP	<5	9 (+)
7	$RuCl_2(C_6H_6)$ + (*R*)-MeO-BIPHEP	<5	4 (–)
8	Ru(methylallyl)$_2$(cod) + (*R*)-MeO-BIPHEP	28	12 (+)
9	Ru(CF_3COO)$_2$(cod) + (*R*)-MeO-BIPHEP	–[d]	n.d.
10	[Rh((*S*)-BINAP)(cod)]BF_4	9	3 (+)
11	[Rh(cat*AS*ium®MQF(*R*))(cod)]BF_4	41	5 (–)
12	[Rh(**A**)(cod)]BF_4[e]	82	rac
13	[Rh(**B**)(cod)]BF_4[e]	16	1 (–)

[a] 0.5 mmol of **1b**, precatalyst 5.0 µmol, H_2, 4 mL of THF, 80 °C, 8.0 MPa, S/Rh = 100, 20 h.
[b] Yields were determined by ^{1}H NMR spectroscopy.
[c] Ee-values were determined by GC analysis.
[d] No *O*-TMS-protected hydrogenation product could be detected by ^{1}H NMR spectroscopy due to decomposition.
[e] Ligands **A** and **B** were recently prepared in the research group of Prof. Börner and shown in Chapter 5.3.

Unfortunately, [Ru(*p*-cymene)((*R*)-C_3-TunePhos)Cl]Cl gave only a low yield and a negligible enantioselectivity of 6 % (entry 1). When (*R*)-4-Tol-BINAP was tested with different Ru precursors, it was not able to decisively raise both, yield and ee-value (entries 2-5), or the product decomposed.

Hydrogenation with (*R*)-MeO-BIPHEP catalyst did also not succeed with respect to conversion and the enantiomeric excess was still poor (entries 6-9).
The rhodium-catalyzed hydrogenation of **1b** was also verified. [Rh(cat*A*Sium®MQF(*R*))(cod)]BF_4 and [Rh(**A**)(cod)]BF_4 yielded best conversions up to 82 % (entry 12), but the stereodiscrimination was poor in all cases (entries 10-13).
It can be summarized that the asymmetric hydrogenation of *O*-trimethylsilyoxy methyl acrylate was accomplished successfully to reach complete conversion. With a Ru catalyst the corresponding *O*-TMS-protected lactate was obtained in 55 %ee that was attained for the first time for this type of product. When the crotonate was applied to the reaction instead of the acrylate, no conversion was noted. Adapting more drastic conditions, conversions up to 82 % could be reached, but the stereodifferentiation still remained low. The relatively small difference in the structure of both substrates seems to have a great influence on reactivity as well as enantioselectivity.

3.1.2 Preparation of chiral *N*,*O*-acetals

Chiral *N*,*O*-acetals often represent essential fragments of a whole range of natural products and pharmaceuticals.[64] The stereochemical importance of the *N*,*O*-acetal subunit, related to the biological activity, is significant and well known today.[64-65]
(–)-Quinocarcin as one representative, found in a culture broth of *Streptomyces melunovinuceus*, is a pentacyclic tetrahydroisoquinoline alkaloid that contains a chiral oxazolidine subsequence (Figure 13).[66] This compound shows activity against Gram-positive bacteria *in vitro* and is moreover antiproliferative against lymphocytic leukemia.[66a-d] Therefore, it is a promising candidate as antitumor antibiotic.[66a,b,e] Psymberin and Myclamide individuals, belonging to the pederin family, possess a *N*,*O*-acetal substructure as well, but only the oxygen is part of a ring and nitrogen is exocyclic.[67] For example, Myclamide E, what belongs to the family of protein synthesis inhibitors,[65a,68] can be isolated from the sponge *Mycale hentscheli*.[69] The myclamide family shows remarkable cytotoxic,[70] antitumor,[68a,b] antiviral,[69] immunosuppressive,[71] antifungal and nematocidal activities.[72] (–)-Zampanolide[73] and Perinadine A[74] have an acyclic hemiaminal and *N*,*O*-acetal structure, respectively, where both heteroatoms are part of the ring structure.
Next to their natural occurrence, *N*,*O*-acetals are used as key intermediates as well. These compounds can be transformed into reactive *N*-imines and subsequently easily attacked by various nucleophiles. In this context, they play an important role for the synthesis of Discorhabdin A.[75]
Although some different methods[76] were already developed for the preparation of *N*,*O*-acetals, however, the synthesis of chiral acyclic[64] and cyclic[77] *N*,*O*-aminal derivatives is limited to an enantioselective Mannich-type reaction catalyzed by a chiral Brønsted acid,[78] up to now.

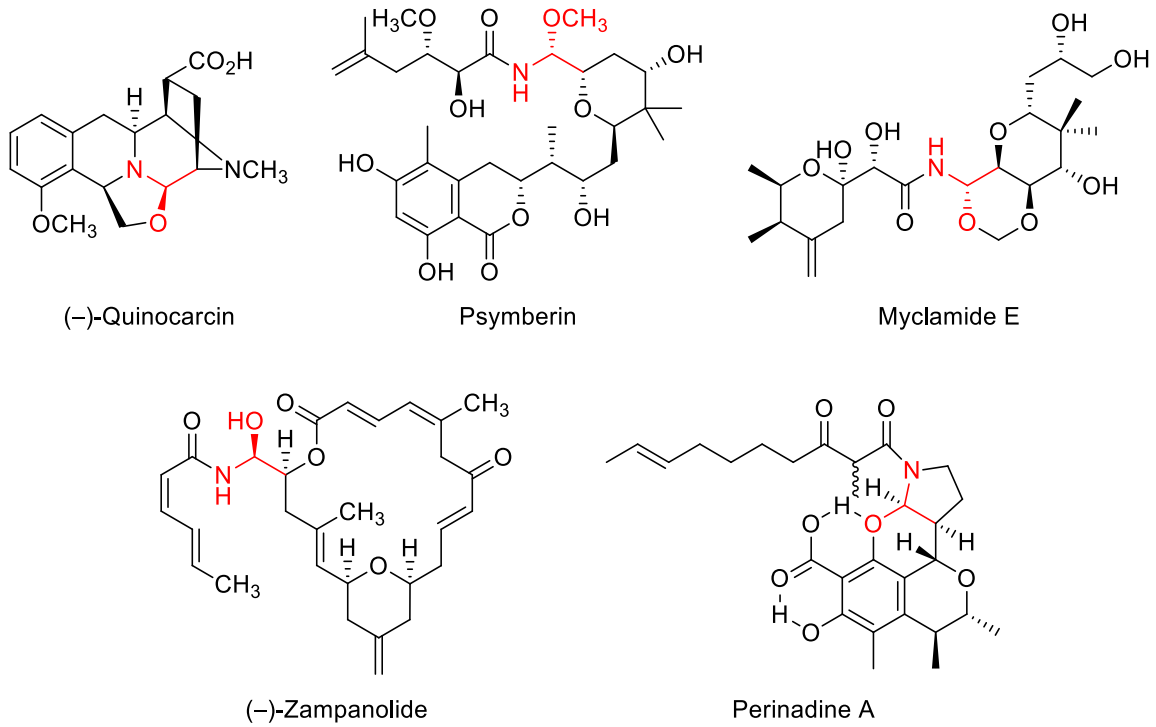


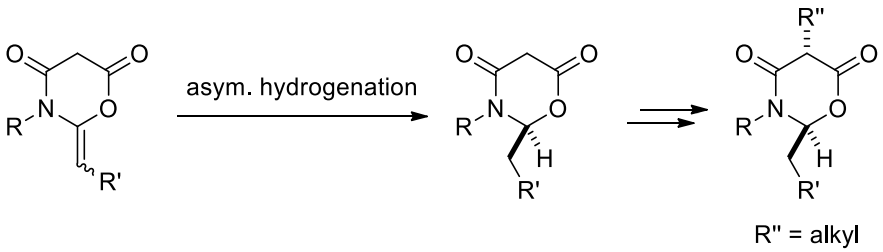
Figure 13. *N*,*O*-Acetals as fragments in naturally occurring compounds: (–)-Quinocarcin, Psymberin, Myclamide E, (–)-Zampanolide and Perinadine A.

The hydrogenation of *N*,*O*-ketene acetals,[i] that can be easily prepared with commercially available reagents, still remains hardly touched so far. In literature there are only two examples for the diastereoselective hydrogenation of a *N*,*O*-ketene acetal on Pd/C.[79]

Hartley *et al.* examined the heterogeneous hydrogenation of *N*-acyl-oxazolone to get chiral oxazolidinones. Disappointingly, the isolated yield of this mixture of diastereomers was only 44 %.[79a]

A substituted 1,3-oxazolidine was hydrogenated heterogeneously by Easton and co-workers with Pd/C. They investigated the stepwise hydrogenation of a *N*,*O*-ketene acetal possessing an additional C-C double bond, but only a low yield of the product was reached.[79b]

The asymmetric hydrogenation of *N*,*O*-ketene acetals has never been accomplished before. It illustrates a great challenge, but could also open new possibilities to get enantiopure *N*,*O*-acetals. Via asymmetric hydrogenation we intended to incorporate a chiral group into a substrate that operates as auxiliary, in order to achieve a diastereoselective alkylation afterwards (Scheme 20).

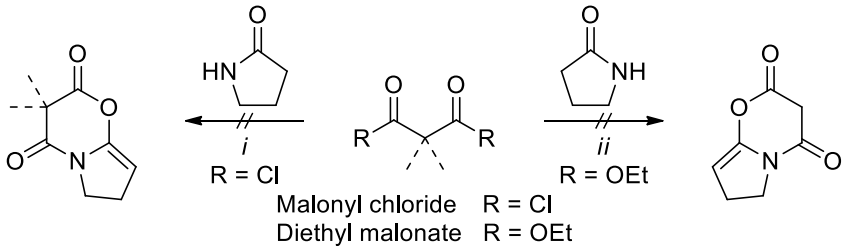


Scheme 20. Generation of a chemical auxiliary via asymmetric hydrogenation followed by diastereoselective alkylation.

[i] A *N*,*O*-ketene acetal is an olefin that bears an electron donating nitrogen and an oxygen atom at the same carbon of the double bond.

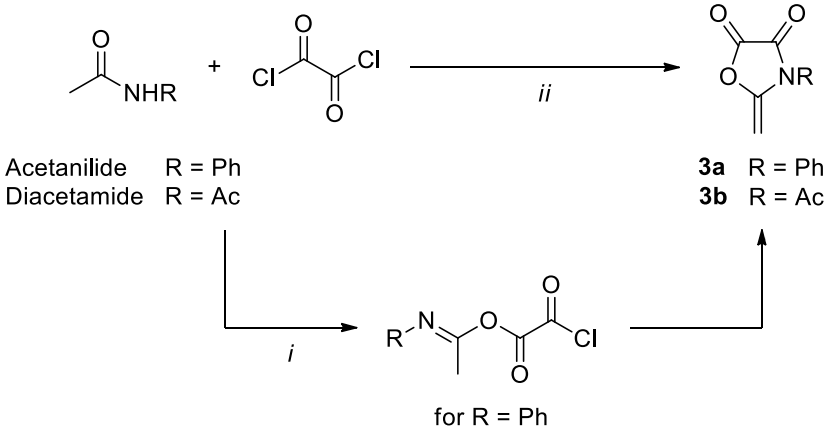
3.1.2.1 Synthesis of *N*,*O*-ketene acetals

At first, it was tried to prepare a prochiral *N*,*O*-ketene acetal from malonyl chloride and 2-pyrrolidone in toluene under reflux for 5 h. Either trials with or without aqueous work-up failed. It can be speculated that additional water acts as a nucleophile and leads to ring opening of the resulting *N*,*O*-ketene acetal. Subsequently, it was necessary to perform the reaction without aqueous work-up.
The reaction in the presence of triethylamine as a base and stirring for 24 h at room temperature was likewise not successful: the starting amide was recovered. Using malonyl diethylester instead of the more reactive chloride, what does not release hydrogen chloride gas, could not be accomplished. Obviously, the 1,3-dicarbonyl compound is stabilized by a shift of the double bond, what makes it less reactive (Scheme 21).
Changing from malonyl to 2,2-dimethyl malonyl and oxalyl chloride, this rearrangement was prevented, but the desired products could only be obtained in traces from the reaction with 2-pyrrolidone and triethylamine at room temperature (Scheme 21, the reaction with oxalyl chloride is omitted). Furthermore, without aqueous work-up, triethylammonium chloride could not be separated completely from the product by filtration, what led back to a reaction without using any base to avoid annoying salt formation.



Scheme 21. Trials for the preparation of a *N*,*O*-ketene acetal: (*i*) toluene, reflux, 5 h *or* 3.0 eq Et_3N, toluene, r.t., 24 h; (*ii*) toluene, reflux, 9 h.

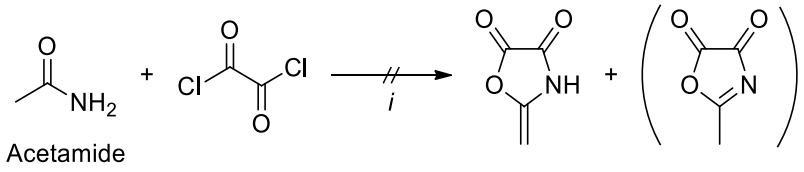
When oxalyl chloride and acetanilide were refluxed in carbon disulfide for 16 h, gas evolution was detected. The product was identified as the mono-attacked acyclic intermediate (92 %). To ensure ring formation and finally to yield the desired *N*,*O*-ketene acetal the reaction time was prolonged to 24 h and benzene was used as solvent with a higher boiling point (Scheme 22).



Scheme 22. Synthesis of *N*,*O*-ketene acetals **3a,b**: (*i*) CS_2, reflux, 16 h; (*ii*) benzene, reflux, 24 h.

Starting from acetanilide and oxalyl chloride in benzene, a brownish precipitate evolved when the reaction mixture was heated under reflux for 24 h. In addition, gas evolution could be obtained. After cooling to room temperature, the solvent was evaporated to yield a puce solid. Purification of the raw

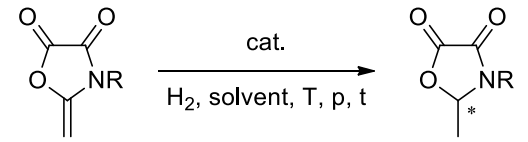
material by column chromatography over silica did not yield final *N*,*O*-ketene acetal **3a**, due to decomposition. For that reason, the solid was distilled under vacuum to give 78 % of **3a** as a white solid.
Employing the same procedure for the symmetric diacetamide[i] and oxalyl chloride gave 77 % of **3b** as a white solid. Both compounds are moisture-sensitive,[ii] but can be stored under argon at 5 °C.
Because reactions with unsymmetric imides would always result in a mixture of both regioisomeres, which is laborious to separate, it was tried to prepare a *N*-unsubstituted *N*,*O*-ketene acetal while substitution at the nitrogen should be realized in a further step. Indeed, no product could be isolated from the reaction of oxalyl chloride and acetamide (Scheme 23).



Scheme 23. Synthesis of a *N*-unsubstituted *N*,*O*-ketene acetal: (*i*) benzene, reflux, 24 h.

3.1.2.2 Asymmetric hydrogenation of *N*,*O*-ketene acetals

The studies were initiated by running the hydrogenation with *N*,*O*-ketene acetals **3a,b**, what possess a phenyl and an acetyl group, respectively, at the nitrogen atom. First of all, the racemic products were isolated from the hydrogenation with heterogeneous rhodium on charcoal (Scheme 24).



3a R = Ph
3b R = Ac

4a R = Ph
4b R = Ac

Scheme 24. Hydrogenation of *N*,*O*-ketene acetals **3a,b**.

The starting material was dissolved in THF and hydrogenated with 2.5 mol% Rh/C catalyst at room temperature and under 0.3 MPa of hydrogen atmosphere for 20 h. The pure product could be obtained quantitatively after separation from the catalyst by filtration and evaporation of the solvent.
Ketene acetals are not stable toward Lewis acids[76a] and undergo ring opening in the presence of a catalytic amount of acid and a nucleophile.[79b,81] Consequently, especially the proper choice of the solvent is very important. For the asymmetric hydrogenation of this substrate aprotic polar solvents, such as THF or DCM, reveal to be appropriate. They enable the complete solubility of both, substrate and catalyst. Moreover, they are not acidic like methanol and do not react as a nucleophile to cleave the *N*,*O*-ketene acetal via ring opening.
As described before, the *N*,*O*-ketene acetals are moisture-sensitive and decomposition can already appear after prolonged standing. For this purpose, a blank test was run to verify the robustness toward the reaction conditions. First of all, 1 mmol of the olefin **3b** and 1 mol% of the achiral catalyst [Rh(dppb)(cod)]BF_4 were dissolved in 4 mL of DCM and the solution was stirred at room temperature under an atmosphere of argon (0.1 MPa) for 20 h. It could be noticed that the initial yellowish solution

[i] Diacetamide was prepared by the reaction of acetamide and acetyl chloride with pyridine as base to yield 85 % of a white solid according to the procedure of Al-Awadi *et. al*.[80]
[ii] Both *N*,*O*-ketene acetals have a slight odor of acetic acid while standing on air.

became yellow, but it was possible to recover the starting material completely. It could be confirmed that the substrate and a homogeneous rhodium catalyst are stable together in solution, even though traces of already formed (acetic) acid are present.
In addition, it was examined, whether the olefin is stable under increased temperature under a hydrogen atmosphere. Two samples of ketene acetal **3b** (each of 1 mmol) were dissolved in THF, temperate to 40 °C and 60 °C, respectively, and stirred for 15 h under 5 MPa of an H_2-atmosphere. As a result, only traces of the corresponding hydrogenation product **4b** could be detected by ^{1}H NMR while the *N*,*O*-ketene acetal **3b** remained stable and was recovered quantitatively.
In an initial test series, an achiral homogeneous rhodium precatalyst [Rh(dppb)(cod)]BF_4 was used to determine the activity toward the transformation of **3b** (Table 6).

Table 6. Hydrogenation of **3b** with 1 mol% [Rh(dppb)(cod)]BF_4 in THF.[a]

Entry	*T* [°C]	*p* [MPa]	Yield[b] [%]
1	40	5.0	Traces
2	40	8.0	Traces
3	60	1.0	–
4	60	2.0	–
5	60	5.0	Traces
6	60	8.0	Traces

[a] 1.0 mmol of **3b**, [Rh(dppb)(cod)]BF_4 10.0 µmol, H_2, 4 mL of THF, *T*, *p*, S/Rh = 100, 3 h.
[b] Yields were determined by ^{1}H NMR spectroscopy.

In principle, almost no conversion could be detected with 1 mol% of [Rh(dppb)(cod)]BF_4 precatalyst at 40 °C and pressures of 5 MPa and 8 MPa, respectively (entries 1,2). At a temperature of 60 °C, but lower pressures, no product can be determined. Even at higher pressures of 5 MPa or 8 MPa, only traces of the desired *N*,*O*-acetal **4b** were found via ^{1}H NMR (entries 5,6). Subsequently, the chiral Rh precatalysts [Rh((*R*)-BINAP)(cod)]BF_4 and [Rh((*S*,*S*)-Me-DuPhos)(cod)]BF_4 were tested in two solvents (THF and DCM) at 60 °C and 5 MPa hydrogen pressure (Table 7).

Table 7. Asymmetric hydrogenation of **3b** with 1 mol% [Rh(PP-ligand)(cod)]BF_4.[a]

Entry	Ligand	Solvent	Yield[b] [%]	ee [%]
1	(*R*)-BINAP	THF	–	n.d.
2	(*R*)-BINAP	DCM	–	n.d.
3	(*S*,*S*)-Me-DuPhos	THF	–	n.d.
4	(*S*,*S*)-Me-DuPhos	DCM	–	n.d.

[a] 0.5 mmol of **3b**, precatalyst 5.0 µmol, H_2, 4 mL of solvent, 60 °C, 5.0 MPa, S/Rh = 100, 20 h.
[b] No yield was determined in any case by ^{1}H NMR spectroscopy.

By means of these results it can be seen that no hydrogenation took place in any solvent under the given conditions. Consequently, more drastic reaction conditions were chosen. The temperature was set to 100 °C and the hydrogen pressure to 10 MPa. THF, having a higher boiling point, was used as reaction solvent instead of DCM (Table 8).

Table 8. Asymmetric hydrogenation of **3b** with 1 mol% catalyst in THF.[a]

Entry	Precatalyst	Yield[b] [%]	ee [%]
1	[Rh((*R*)-BINAP)(cod)]BF_4	–	n.d.
2	[Rh((*R*,*R*)-Me-DuPhos)(cod)]BF_4	–	n.d.
3	[Ru(*p*-cymene)(*R*)-C_3-TunePhos)Cl]Cl	–	n.d.
4	(*R*)-BINAP-$RuCl_2$	–	n.d.

[a] 0.5 mmol of **3b**, precatalyst 5.0 µmol, H_2, 4 mL of THF, 100 °C, 10.0 MPa, S/Rh = 100, 20 h.
[b] No yield was determined in any case by ^{1}H NMR spectroscopy.

Both, rhodium (entries 1,2) as well as ruthenium catalysts (entries 3,4) showed no activity under these conditions. Despite of the variation of the temperature, hydrogen pressure and solvent, the desired product could not be attained. Only the enhancement of the amount of the catalyst from 1 mol% to 5 mol% promised first positive results as illustrated in Table 9.

Table 9. Initial trials of the asymmetric hydrogenation of **3b** with 5 mol% catalyst in THF.[a]

Entry	Precatalyst	*p* [MPa]	Yield[b] [%]	ee[c] [%]
1[d]	[Rh((*R*)-BINAP)(cod)]BF_4	5.0	36	9 (+)
2	[Rh((*R*)-BINAP)(cod)]BF_4	8.0	60	8 (+)
3	[Rh((*R*)-MeO-BIPHEP)(cod)]BF_4	8.0	36	11 (+)
4	[Rh((*S*,*S*)-Me-DuPhos)(cod)]BF_4	8.0	8	26 (+)
5	[Rh((*S*,*S*)-Et-BPE)(cod)]BF_4	8.0	25	50 (+)
6	[Rh((*S*,*S*)-Et-FerroTANE®)(cod)]BF_4	8.0	19	rac
7	[Rh((*R*,*S*)-JosiPhos)(cod)]BF_4	8.0	96	70 (+)
8	[Ru(*p*-cymene)(*R*)-C_3-TunePhos)Cl]Cl	8.0	2	n.d.
9	(*R*)-BINAP-$RuCl_2$	8.0	4	n.d.
10	Ir((*S*,*S*)-Ph_2PThrePHOX)(cod)	8.0	Traces	n.d.

[a] 0.5 mmol of **3b**, precatalyst 25.0 µmol, H_2, 4 mL of THF, 40 °C, *p*, S/Rh = 20, 72 h.
[b] Yields were determined by ^{1}H NMR spectroscopy.
[c] Ee-values were determined by GC analysis.
[d] Reaction time was 20 h.

Taken into account that ee-values frequently can be increased by lowering the temperature, the asymmetric hydrogenation of **3b** was run in THF at 40 °C. The Rh-catalyzed hydrogenation with (*R*)-BINAP as ligand was performed at 5 MPa and 36 % of the corresponding acetal **4b** could be detected in ^{1}H NMR, but with only poor enantioselectivity (entry 1). To increase the reactivity, the pressure was set to 8 MPa and the reaction time was expanded to 72 h while the temperature remained unchanged. The isolated yield could be improved to 60 % without remarkable changes in terms of enantioselectivity (entry 2). For further test series, the hydrogen pressure was regulated to 8 MPa permanently to ensure satisfying yields.
The hydrogenation with the structurally similar Rh/(*R*)-MeO-BIPHEP did not engender any significant improvement of the enantioselectivity (11 %ee) and showed even worse results in the reactivity under the same conditions (entry 3). [Rh((*S*)-Me-DuPhos)(cod)]BF_4 produced only a very low yield of the acetal **4b**, but the enantiomeric excess was improved to 26 % (entry 4). A higher ee-value of 50 % was reached with a rhodium catalyst based on the structurally similar ligand (*S*,*S*)-Et-BPE (entry 5). The best result was attained with the Rh/(*R*,*S*)-JosiPhos catalyst. A yield of 96 % of product **4b** and highest enantiomeric excess of 70 % were reached for the first time (entry 7). Two Ru-complexes and one Ir-complex were also used in the asymmetric hydrogenation of **3b**, but without success (entries 8-10).
Encouraged by the result of the Rh/(*R*,*S*)-JosiPhos catalyst, a series of commercially available ferrocene-based ligands (Figure 14) was screened for the asymmetric hydrogenation of **3b**.

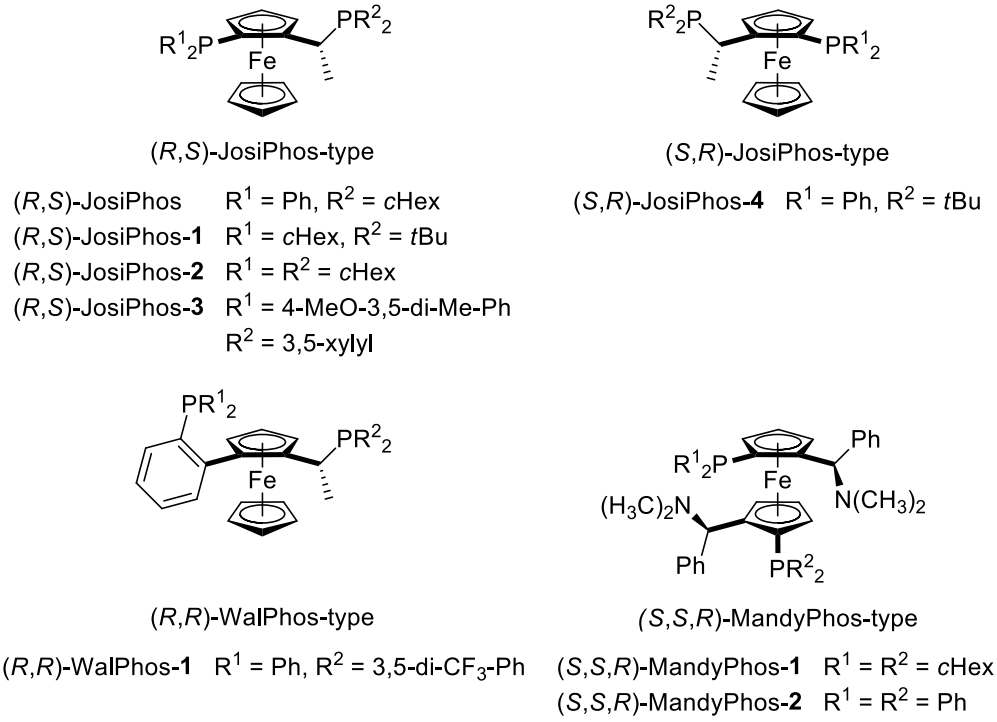


Figure 14. Applied ferrocene-based ligands for the asymmetric hydrogenation of *N*,*O*-ketene acetal **3b**.

The hydrogenation was performed with the previously set conditions (40 °C, 8 MPa hydrogen atmosphere) (Table 10).

Table 10. Screening of ferrocene-based ligands for the asymmetric hydrogenation of **3b** with $[Rh(cod)_2]BF_4$ in THF.[a]

Entry	Ferrocene-based ligand	Yield[b] [%]	ee[c] [%]
1	(*R*,*S*)-JosiPhos	90	70 (+)
2	(*R*,*S*)-JosiPhos-**1**	86	20 (+)
3	(*R*,*S*)-JosiPhos-**2**	87	17 (–)
4	(*R*,*S*)-JosiPhos-**3**	51	53 (–)
5	(*S*,*R*)-JosiPhos-**4**	81	35 (+)
6	(*R*,*R*)-WalPhos-**1**	97	48 (+)
7	(*S*,*S*,*R*)-MandyPhos-**1**	29	14 (+)
8	(*S*,*S*,*R*)-MandyPhos-**2**	37	16 (–)

[a] 0.5 mmol of **3b**, $[Rh(cod)_2]BF_4$ 25.0 µmol, ferrocene-based ligand 27.5 µmol, H_2, 4 mL of THF, 40 °C, 8.0 MPa, S/Rh = 20, 72 h.
[b] Isolated yields after Kugelrohr distillation.
[c] Ee-values were determined by GC analysis.

Various substituents at the phosphorus atom of the ferrocene-based ligands have different influences on the progress of the reaction as well as on the stereoselectivity. Starting with the ligands from the JosiPhos family, the runs showed very good conversion rates and yielded up to 90 % of the desired product (entries 1-3). An influence of the *P*-substituents can also be noted. Interestingly, opposed stereoisomers are preferably formed while using two ligands with the same stereodescriptor (entries 2,3). When steric demanding phenyl groups were linked to the phosphorus, the reactivity decreased while a moderate enantioselectivity was reached (53 %, entry 4).
Changing to the structurally similar WalPhos-type ligand with strongly electron withdrawing CF_3-groups at the phenyl ring, full conversion was observed (entry 6). A yield of 97 % of the product **4b** was isolated with an ee-value of 48 % (entry 6).
Hydrogenation, catalyzed by Rh/MandyPhos-type ligands, gave the acetal in only low yield with negligible enantiomeric excesses (entries 7,8).

The (*R*,*S*)-JosiPhos ligand induced the best result with respect to enantioselectivity. Consequently, an attempt to optimize the reaction by variation of the solvent was carried out. Because the amount of catalyst was significantly high, we attempted to minimize the substrate/rhodium ratio, simultaneously (Table 11).

Table 11. Asymmetric hydrogenation of **3b** with [Rh((*R*,*S*)-JosiPhos)(cod)]BF_4.[a]

Entry	Solvent	S/Rh	*T* [°C]	*p* [MPa]	Yield[b] [%]	ee[c] [%]
1	THF	20	40	8.0	90	70 (+)
2	DCM	20	40	8.0	64	45 (+)
3	EtOAc	20	40	8.0	86	14 (+)
4	Toluene	20	40	8.0	25	31 (+)
5	THF	40	50	10.0	10	18 (+)
6	DCM	40	50	10.0	24	11 (+)
7	EtOAc	40	50	10.0	23	4 (+)
8	Toluene	40	50	10.0	19	8 (+)

[a] 0.5 mmol of **3b**, [Rh((*R*,*S*)-JosiPhos)(cod)]BF_4 12.5-25.0 µmol H_2, 4 mL of solvent, *T*, *p*, S/Rh, 72 h.
[b] Isolated yields after Kugelrohr distillation.
[c] Ee-values were determined by GC analysis.

It can be seen that the solvent has a dramatic influence on the reaction rate. DCM and EtOAc as well as toluene diminish the conversion and seem to have a negative influence on the stereoselectivity of the reaction.
When the amount of catalyst was reduced to 2.5 mol%, the isolated yield of the desired *N*,*O*-acetal **4b** along with its enantiomeric excess declined dramatically in all solvents, even at 50 °C and 10 MPa hydrogen pressure.
In conclusion, this synthesis strategy promotes chiral *N*,*O*-acetals, what can be achieved by a simple two step preparation from inexpensive bulk chemicals. The asymmetric hydrogenation of one representative of the family of *N*,*O*-ketene acetals was carried out for the first time and delivered a chiral *N*,*O*-acetal in 70 %ee and excellent yield of 96 % by using a commercially available Rh catalyst under mild conditions.
The final functionalized *N*,*O*-acetals can be processed further and used for the construction of biologically active compounds.

3.1.3 Preparation of β²-amino acid derivatives[82]

For many years, enantiopure β²-amino acids have played an important role in biochemistry and medicine. These structures can be found as building blocks in several natural products, but also in pharmaceuticals and fine chemicals.[83] β²-Homoalanine, as simplest representative of chiral β²-amino acids, is a substructure (unit C) of naturally occurring cyclic depsipeptides and can be found inter alia in cryptophycins[84] (Figure 15). These compounds are active as antibiotics and display strong cytotoxic activity that is why they are used as promising candidates of anticancer agents.[85]
Chiral 3-amino-2-methylpropanol, derived from β²-homoalanine by reduction of the carboxyl group, can be employed as a synthon for the synthesis of Cyclamenol A.[86] This macrolactame inhibits leukocyte adhesion to endothelial cells and is one of rare non-carbohydrates or peptides of this class.[87] It possesses an anti-inflammatory and anti-infective activity and is used for symptoms related to asthma, arthritis and strokes.[88]

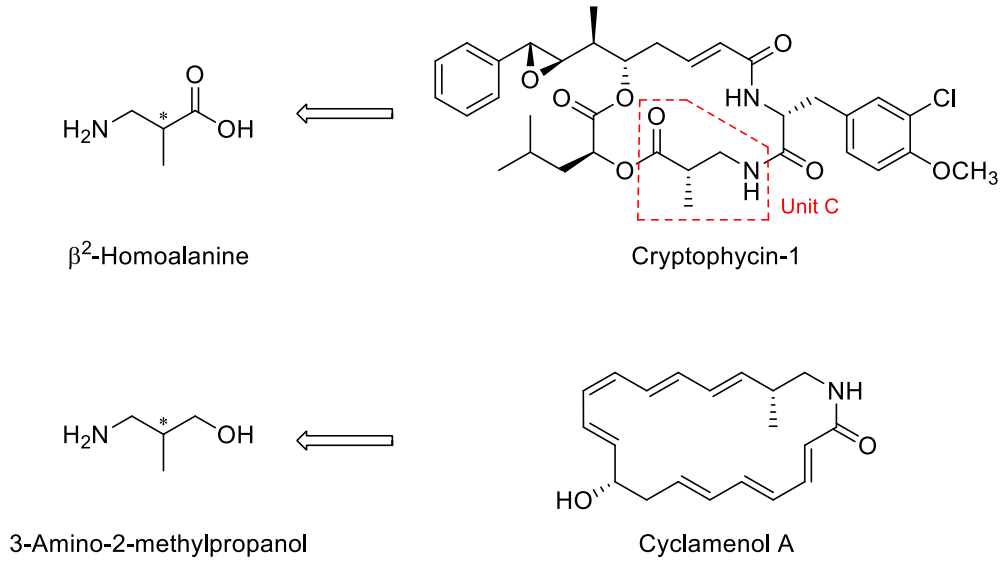


Figure 15. Structures of β²-homoalanine and 3-amino-2-methylpropanol as building blocks for natural compounds Cryctophycin-1 and Cyclamenol A.

Up to now, the synthesis of enantiomerically pure β²-homoalanine derivatives have mainly been focused on starting material from the chiral pool,[84a,87] however, alternative routes, such as chiral resolution[89] and stereoselective alkylation,[90] exist, too.

The asymmetric hydrogenation of dehydro β²-homoalanine has an interesting potential, especially on large industrial-scale. Compared to a great number of routes to β³-homoalanine derivatives,[83a,91] the accessibility of chiral β²-homoalanine and its representatives via catalysis is limited.[92] The preparation of those compounds by the asymmetric hydrogenation of functionalized allylamides was rarely examined in the past and with varying degree of success.[93]

Some publications exist, wherein *N*-phthaloyl-protected olefins were converted with rhodium or ruthenium catalysts and high stereoselectivity.[93a-e] Those publications have in common that non-commercial phosphorus ligands were used, synthesized with much effort. With respect to the subsequent cleavage of the large *N*-phthalimido protecting group, a considerable amount of organic waste is produced, what is disadvantageous in terms of atom efficiency and application on industrial-scale.

Qiu *et al.* examined the asymmetric hydrogenation of *N*-benzyloxy-protected α-aminomethyl acrylates with commercial [Rh(Et-DuPhos)(cod)]BF_4 as precatalyst and reached ee's up to 83 %.[93f] *N*-Boc-protected allylamides were employed in asymmetric hydrogenation by Stephan *et al.* using a self-prepared chiral ligand related to DIPAMP, called *t*Bu-SMS-Phos.[93g]

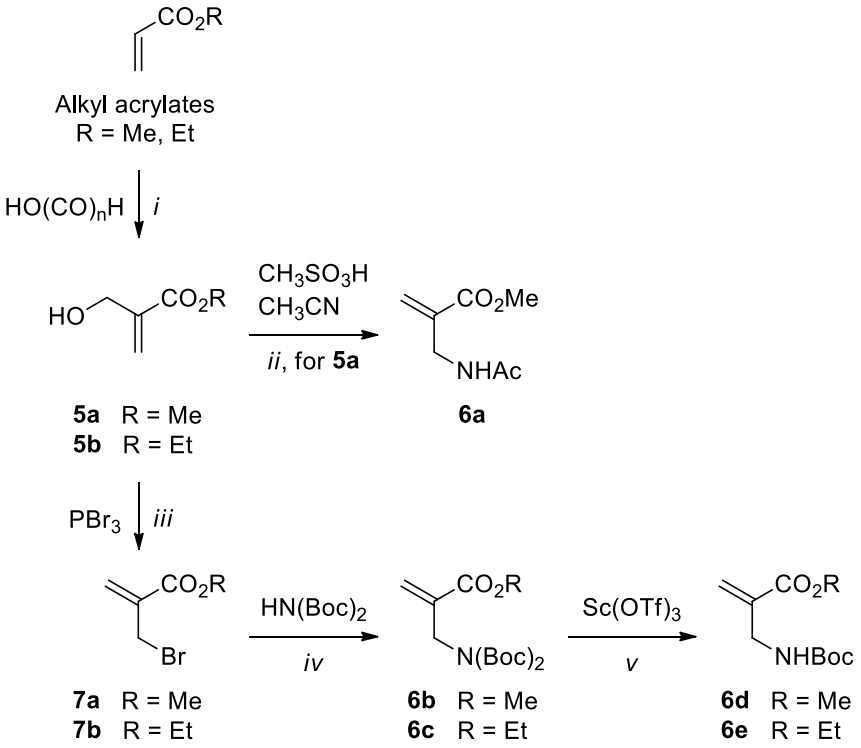
Furthermore, to the best of our knowledge, there is only one example for the asymmetric hydrogenation of *N*-acetyl derivatives. Robinson *et al.* performed a reaction with commercially available (*R*,*R*)-Me-BPE, but reached poor enantioselectivities (up to 33 %). Moreover, long reaction times were required.[93h]

Working group of Börner investigated the preparation of *N*-benzyl- and *N*-Boc-protected alkyl 2-aminomethyl-3-aryl-propanoates via a Rh-catalyzed asymmetric hydrogenation,[93i] but the synthesis of simple enantiopure β²-homoalanine by asymmetric hydrogenation still remains a challenge.

3.1.3.1 Synthesis of dehydro β²-homoalanine derivatives

First of all, starting from methyl and ethyl acrylate, respectively, 2-hydroxymethyl acrylates **5a,b** could be synthesized in a Baylis-Hillmann reaction with an excess of paraformaldehyde.[94] These

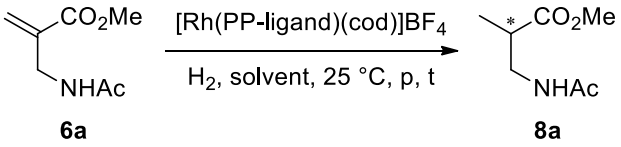
compounds were obtained in 43 % (**5a**) and 70 % (**5b**) yield, respectively, as colorless, viscous oils after column chromatography. Compound **5a** served as educt for the synthesis of *N*-acetyl-protected derivative **6a** by reaction with acetonitrile in the presence of methanesulfonic acid. The nitrogen attacks the terminal side of the C=C bond and the double bond rearranges by elimination of water. After aqueous work-up and subsequent flash chromatography, **6a** yielded as white solid in 47 %.[95] This compound is hygroscopic and can be stored for several days under argon at -20 °C.
When Baylis-Hillmann adducts **5a,b** were reacted with tribromo phosphine, the corresponding halogenated olefins **7a,b** could be isolated in 89 % and 67 %, respectively.[96] By reaction with di-*tert*-butyl iminodicarboxylate, they were transferred into the di-*N*-Boc-protected derivatives **6b,c**, which were isolated without further purification (95 % and 99 % yield). When these compounds were treated with scandium(III) triflate, the monoprotected compounds **6d,e** were formed. Both could be obtained in 84 % yield after column chromatography.[97]



Scheme 25. Synthesis of varying *N*-protected, prochiral dehydro β²-homoalanine derivatives **6a-e**: (*i*) 1.0 eq DABCO, dioxane/water (*v*:*v* 1:1), r.t., 72 h; (*ii*) K_2CO_3, 60 °C → 110 °C, 6 h; (*iii*) Et_2O, 0 °C → r.t., 2 h; (*iv*) 1.5 eq K_2CO_3, CH_3CN, r.t., 72 h; (*v*) THF, r.t., 24 h.

3.1.3.2 Enantioselective hydrogenation of dehydro β²-homoalanine derivatives

Methyl 2-(acetamidomethyl)acrylate **6a** was exemplarily taken as a test substrate for asymmetric hydrogenation. Catalysts were prepared from a commercially available precatalyst of the type [Rh(PP-ligand)(cod)]BF_4 under hydrogen atmosphere and in the presence of the prochiral substrate with a substrate/rhodium ratio (S/Rh) of 100/1 (Scheme 26).



6a **8a**

Scheme 26. Asymmetric hydrogenation of dehydro β^2-homoalanine derivative **6a**.

Ligands, previously proved for the asymmetric hydrogenation of structurally similar compounds, were chosen.[93f,h,i] In general, the reaction with chiral diphospholane ligands showed most promising results (Table 12).

Table 12. Initial trials of the asymmetric hydrogenation of **6a** with [Rh(PP-ligand)(cod)]BF_4.[a]

Entry	Ligand	Solvent	*p* [MPa]	ee[b] [%]
1[c]	(*S*,*S*,*R*,*R*)-TangPhos	MeOH	2.5	29 (*S*)
2	(*S*,*R*)-JosiPhos	MeOH	2.5	28 (*R*)
3	(*S*,*S*)-Et-DuPhos	MeOH	2.5	92 (*R*)
4	cat*AS*ium®MQF(*R*)	MeOH	2.5	57 (*S*)
5	(*S*,*S*)-Me-BPE	MeOH	2.5	29 (*R*)
6[d]	cat*AS*ium®MQF(*R*)	MeOH	0.1	21 (*S*)
7[e]	cat*AS*ium®MQF(*R*)	DCM	0.1	89 (*S*)
8	cat*AS*ium®MQF(*R*)	DCM	2.5	>99 (*S*)
9	cat*AS*ium®MQF(*R*)	THF	2.5	23 (*S*)
10[c]	(*S*,*S*,*R*,*R*)-TangPhos	DCM	2.5	14 (*S*)
11	(*S*,*S*)-Me-DuPhos	DCM	2.5	5 (*R*)
12	(*S*,*S*)-Et-DuPhos	DCM	2.5	68 (*R*)
13	(*S*,*S*)-*i*Pr-DuPhos	DCM	2.5	rac
14	(*S*,*S*)-Me-BPE	DCM	2.5	41 (*R*)

[a] 0.33 mmol of **6a**, [Rh(PP-ligand)(cod)]BF_4 3.3 µmol, H_2, 4 mL of solvent, 25 °C, 0.1 MPa, S/Rh = 100, 20 h.
[b] Full conversion was observed in all cases, determined by ^{1}H NMR spectroscopy; ee-values were determined by GC analysis.
[c] Side product **9a** (*vide infra*) was observed by ^{1}H NMR spectroscopy (6 % and 22 %).
[d] Reaction time was 6 h.
[e] Reaction time was 20 min.

All reactions proceeded with full conversion. When the hydrogenation was performed in methanol, ligands like (*S*,*S*,*R*,*R*)-TangPhos and (*S*,*R*)-JosiPhos gave only poor enantioselectivities (entries 1,2). Hydrogenation with (*S*,*S*)-Et-DuPhos as ligand resulted in the best stereodifferentiation with 92 %ee (entry 3). Structurally related ligands could not improve the stereoselectivity under the same conditions (entries 4,5). Changing to THF and DCM, respectively, enormously affected the stereoselectivity. Highest ee-values could be achieved with a Rh[cat*AS*ium®MQF(*R*)] precatalyst in DCM[91a] (entry 8) when the hydrogen pressure was 2.5 MPa. A comparison between the structurally similar ligand DuPhos and cat*AS*ium®MQF(*R*) shows only a slight difference in the steric, but the more in the electronic structure. While the phosphorus atoms of the DuPhos ligand are attached to a benzene ring, cat*AS*ium®MQF(*R*) possesses a four-membered ring as backbone bearing four strong electron withdrawing fluorine atoms. Therefore, the electron density at the phosphorus is reduced, what has a positive effect on the asymmetric hydrogenation. An enantiomeric excess up to >99 % could be reached. In some cases, also the isomerized side product **9a** was detected (entries 1,10).
With the Rh[cat*AS*ium®MQF(*R*)] precatalyst in hand we tried to optimize other reaction parameters (time, pressure of H_2, S/Rh) (Table 13).

Table 13. Optimization of the reaction conditions for the asymmetric hydrogenation of **6a** with [Rh(cat*A*Sium®MQF(*R*))(cod)]BF_4 in DCM.[a]

Entry	S/Rh	*p* [MPa]	*t* [h]	Conversion[b] [%]	ee[c] [%]
1	100	2.5	20	>99	>99
2	200	2.5	1.5	>99	>99
3	500	2.5	4.5	>99	>99
4	500	2.5	0.2	>99	>99
5[d]	1000	2.5	4.5	>99	54
6	1000	5.0	4.5	>99	99
7[d]	2000	5.0	20	92	11
8[d]	1000	15.0	20	89	69
9[d]	1500	15.0	20	83	39
10[d]	1750	15.0	20	75	12
11[d]	2000	15.0	20	64	18
12[e]	300	5.0	3	>99	99

[a] 0.33 mmol of **6a**, [Rh(cat*A*Sium®MQF(*R*))(cod)]BF_4 0.17-3.3 µmol, H_2, 4 mL of DCM, 25 °C, *p*, S/Rh, *t*.
[b] Conversions were determined by ^{1}H NMR spectroscopy.
[c] Ee-values of the (*S*)-enantiomer were determined by GC analysis.
[d] Side product **9a** (*vide infra*) was observed by ^{1}H NMR spectroscopy (4-15 %).
[e] Up-scale to 1.0 g of substrate.

At first, we reduced the amount of the catalyst and increased the substrate/rhodium ratio from 100/1 to 500/1, while adjusting the reaction time, simultaneously (entries 1-4). Fortunately, no decline in the conversions or enantioselectivities was noted. Even with a ratio of S/Rh = 500 the reaction time could be drastically reduced to 20 min without any loss of yield of the desired product (entry 4). Further increase of the S/Rh ratio to 1000/1 influenced the selectivity (54 %ee, entry 5). This can be rationalized by the fact that the external double bond migrates and isomeric olefins (*E*)-**9a** and (*Z*)-**9a** are formed (the shifts of the signals in ^{1}H NMR can be compared to those of the ethyl ester,[93a] (Scheme 27). It can be supposed that these enamides are hydrogenated likewise but with lower enantioselectivity, what decreases the overall enantiomeric excess. Both isomers, (*E*)-**9a** and (*Z*)-**9a**, could be identified in the final mixture, what gives evidence for this assumption.
To avoid any loss of stereoselectivity, when a S/Rh ratio of 1000/1 is used, the H_2-pressure was increased to 5 MPa (entry 6). With a lower catalyst amount, the conversion and also the enantioselectivity declined (entries 7-11). Up-scaling to 1 g of the substrate was successfully accomplished at a S/Rh ratio of 300 (entry 12). With the optimized conditions it was possible to hydrogenate *N*-Boc-protected substrates **6b-e** (Table 14).

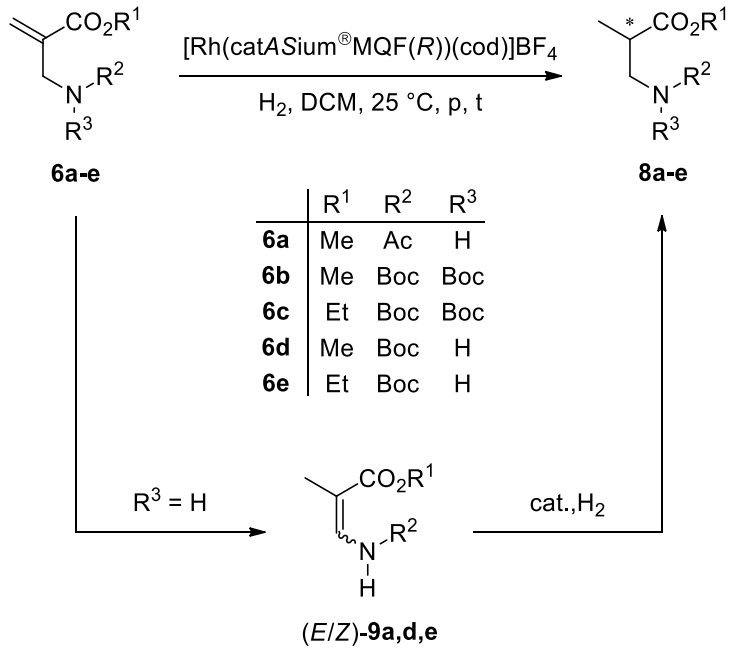
Table 14. Scope of the asymmetric hydrogenation of **6b-e** with [Rh(cat*A*Sium®MQF(*R*))(cod)]BF_4 in DCM.[a]

Entry	Substrate	*p* [MPa]	*t* [h]	Conversion[b] [%]	ee[c] [%]
1	**6b**	2.5	20	38	77 (+)
2	**6b**	5.0	20	55	75 (+)
3	**6c**	2.5	20	34	81 (+)
4	**6c**	5.0	20	43	73 (+)
5[d]	**6d**	2.5	1	39	91 (*S*)
6[d]	**6d**	2.5	3	45	90 (*S*)
7[d]	**6d**	2.5	20	42	87 (*S*)
8[d]	**6d**	5.0	3	42	83 (*S*)
9	**6d**	5.0	20	>99	83 (*S*)
10[e]	**6d**	8.0	20	>99	94 (*S*)
11[d]	**6d**	1.0	3	52	86 (*S*)
12[d]	**6e**	2.5	1	83	89 (*S*)
13	**6e**	2.5	3	>99	88 (*S*)
14	**6e**	2.5	20	>99	87 (*S*)
15	**6e**	5.0	3	>99	83 (*S*)
16	**6e**	1.0	3	>99	91 (*S*)
17	**6e**	0.1	3	>99	96 (*S*)

[a] 0.33 mmol of substrate, [Rh(cat*A*Sium®MQF(*R*))(cod)]BF_4 3.3 µmol, H_2, 4 mL of DCM, 25 °C, *p*, S/Rh = 100, *t*.
[b] Conversions were determined by ^{1}H NMR spectroscopy.
[c] Absolute configuration of **6b** and **6c** could not be determined clearly. The sign of the specific rotation was positive. The positive sign of the specific rotation for **6d** and **6e** corresponds to their (*S*)-enantiomers; ee-values were determined by GC or HPLC analysis.
[d] Side products **9d** and **9e** (*vide infra*) were observed by ^{1}H NMR spectroscopy (3-15 %).
[e] S/Rh = 50.

In general, the asymmetric hydrogenation of di-*N*-Boc-protected acrylates **6b,c** proved to be more difficult (entries 1-4). The conversions of these substrates were only moderate although the reactions were performed for 20 h. Doubling the pressure from 2.5 to 5 MPa slightly raised the conversion, however, affected the enantioselectivity (entries 2,4). For these substrates only moderate ee-values could be reached. Changing to the mono-*N*-Boc-protected substrate **6d** led to improved enantioselectivities, but the conversions were still low, despite of extension of the reaction times (entries 5-7). Full conversion was reached with a hydrogen pressure of 5 MPa without any side reactions after 20 h (entry 9). Unfortunately, the enantioselectivity fell to 83 %. The best result (full conversion, 94 %ee) was reached with a hydrogen pressure of 8 MPa and a substrate/rhodium ratio of 50 (entry 10).
For ethyl acrylate **6e** full conversion was already achieved after 3 h at a hydrogen pressure of 2.5 MPa. (entry 13). When the H_2-pressure was increased to 5 MPa, the enantioselectivity dropped to 83 %. Finally, a lower hydrogen pressure of 1 MPa and 0.1 MPa, respectively, had a positive effect on the stereoselectivity (91 %ee and 96 %ee). Furthermore, in some cases, the external double bond migrates to the internal position to form (*E*)- and (*Z*)-isomers as already mentioned for **6a** (Scheme 27). These corresponding enamides **9d,e** could be found in the final mixtures up to 3-15 mol% (entries 5-8,11,12). This effect could be observed especially in solvents like THF and MeOH. In asymmetric hydrogenation this isomerization causes incomplete hydrogenation and also drastically reduced enantioselectivities.[i] Surprisingly, an enantiomeric excess of only 4 % was detected when the hydrogenation of **6d** was performed with Rh/(*S*,*S*)-Et-DuPhos under standard conditions (25 °C, 2.5 MPa, 20 h) in methanol. 85 % of the substrate were converted, but at least 10 % thereof isomerized (not shown in Table 14).

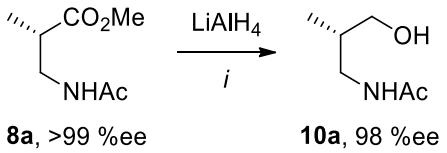
[i] Such migration was already described by Yamamoto with the related *N*-methoxycarbonyl substrate.[98]



Scheme 27. Asymmetric hydrogenation of derivatives **6a-e** and concomitant isomerization.

3.1.3.3 Synthesis of chiral secondary products

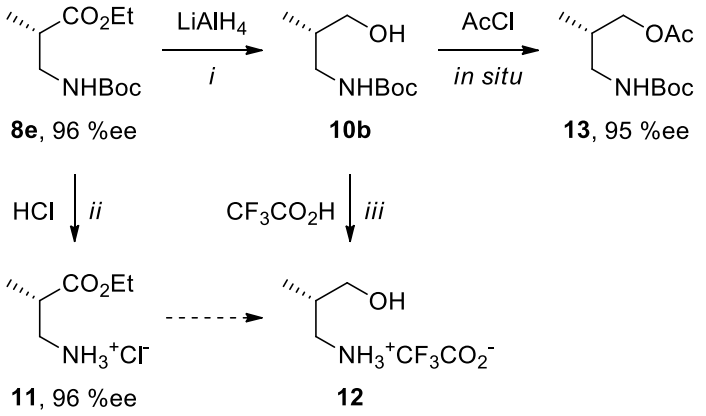
N-Acetyl-protected 3-amino-2-methylpropanol[99] **10a** can be generated by reduction of *N*-acetyl derivative **8a**. Therefore, this compound served as a model substrate with >99 %ee, which was taken from the enantioselective hydrogenation of **6a** (Table 12, entry 8). At first, the ester group was selectively reduced by using $LiAlH_4$ at 0 °C within 2 h to give corresponding alcohol **10a**. Fortunately, under these conditions, the *N*-acetyl group was not affected and the chiral integrity remained almost intact (98 %ee, Scheme 28).



Scheme 28. Reduction of the ester group of chiral hydrogenation product **8a**: (*i*) THF, 0 °C, 2 h.

When the reaction time was extended to 4 h, the *N*-acetyl moiety was also reduced to give (*S*)-3-(ethylamino)-2-methylpropan-1-ol (**10a'**, 11 % visible in the crude mixture together with **10a**).
The *N*-Boc-protected ester **8e** (96 %ee, Table 14, entry 17) could be likewise reduced with $LiAlH_4$ at 0 °C within 5 h to give amino alcohol **10b**. The enantiomeric excess of *O*-acetyl derivative **13**, obtained by *in situ* treatment of **10b** with acetyl chloride, retained in comparison to ester **8e** (95 %ee, Scheme 29).
To remove the *N*-Boc-protection group of **10b** the alcohol was treated with trifluoroacetic acid in dichloromethane to yield the corresponding chiral deprotected ammonium salt **12** of the amino alcohol with 95-96 %ee. Alternatively, the *N*-Boc group of ester **8e** could be removed firstly when treated with HCl/dioxane. Hydrochloride **11** of the amino acid ester was generated this way under complete preservation of the enantioselectivity (96 %ee). Followed reduction of the ester group was performed

with $LiAlH_4$ and $NaBH_4$, respectively. Unfortunately, the reaction was accompanied by the formation of several by-products and did not yield the corresponding alcohol.



Scheme 29. Further reactions of chiral hydrogenation product **8e**: (*i*) THF, 0 °C → r.t., 5 h; (*ii*) dioxane, r.t., 2 h; (*iii*) DCM, r.t., 3 h.

In conclusion, it was possible to prepare enantiopure 2-methyl-β-alanine (β^2-homoalanine) derivatives via enantioselective hydrogenation by using the commercially available precatalyst ([Rh(cat*AS*ium®MQF(*R*))(cod)]BF_4) under mild conditions. Furthermore, this route tolerates different ester groups as well as different *N*-protecting groups. This fact is especially precious with regard to the great variation possibilities for the construction of peptides and potential biologically active compounds.

It was also possible to transform the β^2-homoalanine into chiral *N*-protected 3-amino-2-methylpropanol derivatives to get a valuable building block.

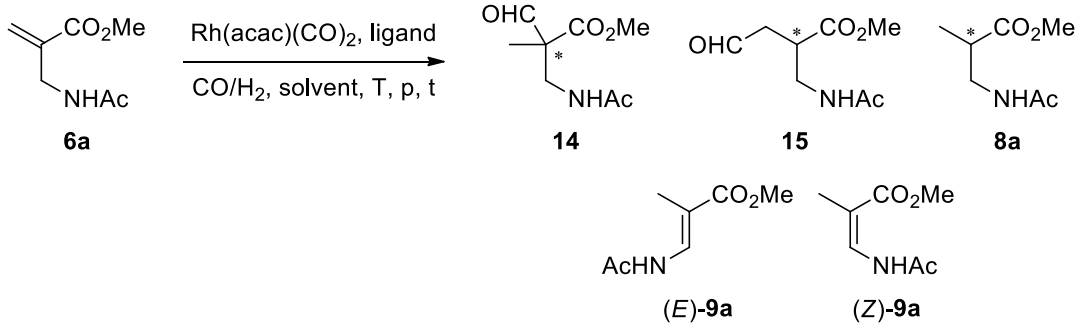
3.2 Hydroformylation

3.2.1 Preparation of functionalized β^2-homoalanine derivatives

The successful asymmetric hydrogenation of dehydro β^2-homoalanine derivatives prompted us to undertake more investigations, what led to the asymmetric hydroformylation of this substrate class. Independently, what side of the double bond is mainly attacked, we expected a chiral carbonyl compound that could serve as a building block for a range of interesting functionalized compounds (e.g. chiral substituted mixed malonic acid ester).

3.2.1.1 Asymmetric hydroformylation of dehydro β^2-homoalanine derivatives

From the hydroformylation of methyl 2-(acetamidomethyl)acrylate **6a**, different products can result. Next to both aldehydes, **14** (branched aldehyde) and **15** (linear aldehyde), the hydrogenation product **8a** as well as the isomerized olefins (*E*)-**9a** and (*Z*)-**9a** should be taken into consideration (Scheme 30).



Scheme 30. Hydroformylation of dehydro β[2]-homoalanine derivative **6a**.

We started our trials with non-asymmetric hydroformylation and used achiral phosphine and phosphite ligands under several conditions (Table 15).

Table 15. Initial trials of the Rh-catalyzed non-asymmetric hydroformylation of **6a**.[a]

Entry	Ligand	*T* [°C]	*p* [MPa]	14[b] [%]	15[b] [%]	8a[b] [%]	(*E*)-9a[b] [%]	(*Z*)-9a[b] [%]
1	PPh_3	100	5.0	–	–	–	17	83
2	$P(OPh)_3$	60	2.0	5	–	–	9	86
3[c]	BiPhePhos	60	2.0	4	–	15	16	66
4[d]	$P(OPh)_3$	30	2.0	50	–	4	5	41

[a] 1.0 mmol of **6a**, Rh(acac)$(CO)_2$ 10.0 µmol, ligand 30.0 µmol, CO/H_2 = 1:1, 5 mL of toluene, *T*, *p*, S/Rh = 100, 21 h.
[b] Full conversion was observed in all cases; yields were determined by ^{1}H NMR spectroscopy.
[c] Ligand 12.0 µmol.
[d] Reaction time was 65 h; ligand 60.0 µmol.

In a first trial, the hydroformylation was performed at 100 °C and under syngas atmosphere of 5 MPa with Rh(acac)$(CO)_2$ and triphenylphosphine as ligand. Although full conversion occurred, neither aldehydes nor the hydrogenation product were detected. The substrate was completely converted into the isomerized (*E*)- and (*Z*)-olefin (entry 1). Under milder conditions (60 °C, 2 MPa syngas), using the monodentate ligand triphenylphosphite, 95 % of the isomerization product were generated, but also a small amount of the *iso*-aldehyde could be detected. When the bidentate BiPhePhos was employed, 15 % of hydrogenation product **8a** were formed, but the quantity of the branched aldehyde was still low and the linear aldehyde could not be determined at all. Unfortunately, the isomerization products represented the main part of the product mixture (82 %, entry 3).
While reducing the temperature to 30 °C, the reaction time was extended to 65 h to ensure full conversion. When Rh/$P(OPh_3)_3$ was used, the amount of the isomerized olefins could be reduced to 5 % ((*E*)-**9a**) and 41 % ((*Z*)-**9a**), respectively, whereas the amount of the branched aldehyde raised up to 50 %.
When trisubstituted olefin (*E*)-**9a** was hydoformylated with the rhodium catalyst, using triphenylphosphine at 100 °C and 5 MPa, no reaction occurred and the starting material was recovered quantitatively (^{1}H NMR, not shown in Table 15). This makes clear that the isomerized olefin does not react further to the aldehyde under the given conditions.
The asymmetric variant of the hydroformylation of **6a** was performed under mild conditions (Table 16). At first, we accomplished the reaction at 60 °C with a range of commerically available bidentate phosphorus ligands. Afterwards, these trials were repeated at 30 °C to see any differences, especially in the degree of isomerization and enantioselectivity.

Table 16. Initial trials of the Rh-catalyzed asymmetric hydroformylation of **6a** with commercial ligands.[a]

Entry	Ligand	*T* [°C]	*t* [h]	Conv.[b] [%]	**14**[b] [%]	**15**[b,c] [%]	**8a**[b] [%]	(*E*)-**9a**[b] [%]	(*Z*)-**9a**[b] [%]	ee[d] [%]
1	(*S*,*S*)-DIOP	60	21	100	28	–	2	21	48	18 (+)
2	(*R*,*R*)-DIPAMP	60	21	100	12	–	72	4	12	18 (–)
3	(*R*,*R*)-Me-DuPhos	60	21	95	20	–	25	20	30	1 (–)
4	(*S*,*S*)-ChiraPhos	60	21	100	10	–	57	6	27	n.d.
5	(*R*,*R*)-Chiraphite	60	21	100	4	–	47	10	39	n.d.
6	(*R*,*R*)-QuinoxP*	60	21	99	89	–	6	4	–	10 (–)
7	(*R*,*R*,*S*)-BisDiazaPhos	60	21	100	13	–	–	20	67	2 (–)
8	(*S*,*S*)-DIOP	30	65	70	51	–	2	4	13	33 (+)
9	(*R*,*R*)-DIPAMP	30	65	86	2	–	63	6	15	n.d.
10	(*R*,*R*)-Me-DuPhos	30	65	88	<1	<1	77	4	6	n.d.
11	(*S*,*S*)-ChiraPhos	30	65	79	4	–	42	5	28	n.d.
12	(*R*,*R*)-QuinoxP*	30	65	79	13	<1	35	10	21	1 (+)
13	(*R*,*R*)-Chiraphite	30	65	76	6	<1	44	7	19	n.d.
14	(*R*,*R*)-Kelliphite	30	65	100	4	1	55	10	30	4 (+)
15	(*R*,*R*)-Ph-BPE	30	65	100	4	–	65	6	25	6 (+)

[a] 0.5 mmol of **6a**, $Rh(acac)(CO)_2$ 5.0 µmol, PP-ligand 6.0 µmol, CO/H_2 = 1:1, 5 mL of toluene, *T*, 2.0 MPa, S/Rh = 100, *t*.
[b] Conversions and yields were determined by ^1H NMR spectroscopy.
[c] Due to the small amount in the final mixture, the amount of the linear aldehyde (**15**) was determined by integration of the characteristic signal for the proton of the aldehyde group (δ = 9.39 ppm) in ^1H NMR spectrum.
[d] Ee-values of the branched aldehyde (**14**) were determined by GC analysis.

It can be summarized that the hydroformylation reactions, performed at 60 °C, provided almost full conversion in all cases (entries 1-7). When (*S*,*S*)-DIOP was used as ligand, the isomerization products can be observed next to the branched aldehyde. The enantiomeric excess of **14** was poor (18 %ee). When (*R*,*R*)-DIPAMP was employed to the reaction, the isomerization was suppressed, but competitive hydrogenation eventuated (72 %). Hydroformylation with (*R*,*R*)-Me-DuPhos as well as with (*S*,*S*)-ChiraPhos as ligand emerged with either a significant amount of isomerized or hydrogenated substrate. Additionally, a disatisfactionary amount of the desired aldehyde and no considerable stereodifferentiation could be obtained (entries 3,4). Ligand (*R*,*R*)-QuinoxP* induced a good selectivity toward the formation of the branched aldehyde, however, the ee-value was negligible (10 %ee). Interestingly, only a small amount of the hydrogenation product was detected and isomerization hardly occurred (entry 6). The Rh/(*R*,*R*,*S*)-BisDiazaPhos catalyst has a pronounced property to isomerize **6a**. Furthermore, the yield of almost racemic *iso*-aldehyde was poor (13 %).
With a reduced temperature (30 °C), but longer reaction time, full conversion could not be detected in any case. For (*S*,*S*)-DIOP, these conditions seem to have a positive effect on the yield of the branched aldehyde (51 %). Also the enantiomeric excess increased to 33 %. Hydrogenation and also isomerization were repressed to minor side reactions. Obviously, a lower temperature suppressed isomerization, but it forced hydrogenation in some cases (entries 9-11).

For both chiral diphosphines (*R*,*R*)-QuinoxP* and (*R*,*R*)-Ph-BPE as well as the diphosphites (*R*,*R*)-Chiraphite and (*R*,*R*)-Kelliphite, low temperature does not have a positive effect on the enantioselectivity so that almost racemic mixtures were detected (entries 12-15).
In a short summary it can be concluded that **6a** is a poor substrate for asymmetric hydroformylation. Because of an additional methylene group, located next to the olefin, the double bond can easily rearrange that leads to a three-fold and therefore thermodynamically more stable olefin. The isomerized olefin does not undergo hydroformylation. Furthermore, reduction of the temperature had a great influence on the conversions of **6a**, but required very long reaction times.
For that reason, we expanded our examination in the asymmetric hydroformylation of α-substituted styrenes, which cannot isomerize.

3.2.2 Preparation of chiral 3-aryl-3-phosphorylated propanals

For a long time, chiral phosphorus compounds have become more and more important to chemical application and attracted special attention. Next to the valuable role of chiral phosphines in the metal-catalyzed asymmetric catalysis, phosphonic acids are used as pharmaceuticals and pesticides.[100]
Among a variety of organocatalytic asymmetric hydrophosphination of cinnamaldehyde derivatives,[101] the preparation of chiral phosphonates, using this method, were exclusively discussed by Córdova and co-workers in 2008.[101a] Although they reached ee's up to 95 % for corresponding phosphine oxides, which were also synthesized, the enantioselectivities for the phosphonates were quite low (up to 14 %ee, Figure 16).

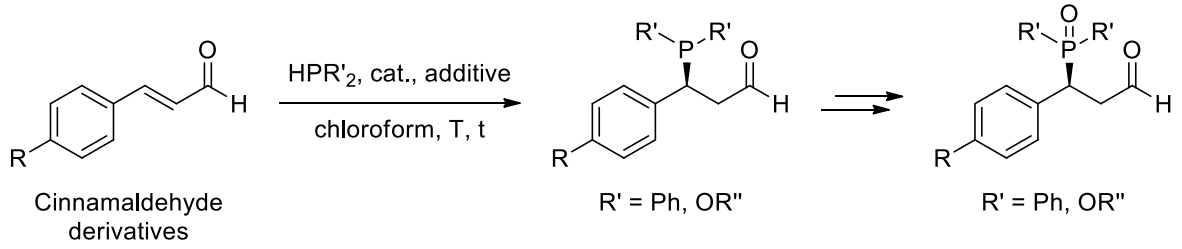
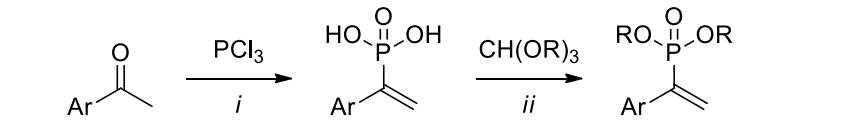


Figure 16. Organocatalytic asymmetric hydrophosphination of cinnamaldehyde derivatives by Córdova.

This prompted us to find another route for the preparation of 3-aryl-3-phosphorylated propanals. Herein we disclose the first example of the rhodium-catalyzed asymmetric hydroformylation of α-phosphorylated vinyl arenes.

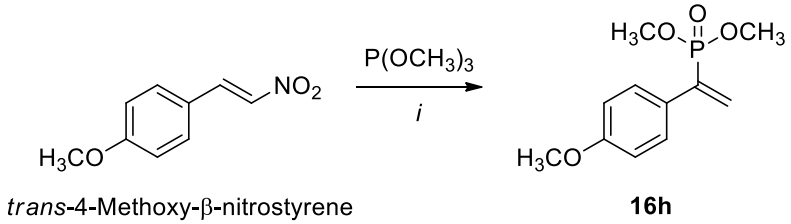
3.2.2.1 Synthesis of α-phosphorylated vinyl arenes

Prochiral phosphonic acids were prepared from substituted acetophenones or 2-acetonaphthone and phosphorus trichloride in the presence of concentrated acetic acid under reflux. In case of 2',4',6'-trimethylacetophenone, no product could be isolated under these conditions. These vinyl compounds were transformed into the corresponding esters by stirring with an excess of trialkyl orthoformate at 50 °C for 2 h, followed by column chromatography, according to the procedure of Genêt.[102] The prochiral phosphonates **16a-g** were attained as colorless oils and white solids in 41-84 % yield (Scheme 31).



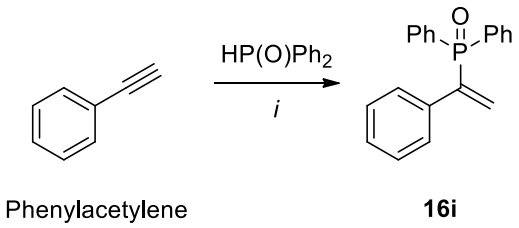
Scheme 31. Preparation of phosphonates **16a-g**: (*i*) HOAc, 0 °C → r.t., 16 h, then H_2O, reflux, 2 h; (*ii*) 100 °C, 2 h.

For the synthesis of 4-methoxy derivative **16h**, another synthesis was used. According to the procedure of Ding,[103] *trans*-4-methoxy-β-nitrostyrene was reacted with trimethyl phosphite over 9 d at room temperature to yield **16h** as a yellowish oil after column chromatography in 69 % (Scheme 32).



Scheme 32. Preparation of phosphonate **16h**: (*i*) DME, r.t., 9 d.

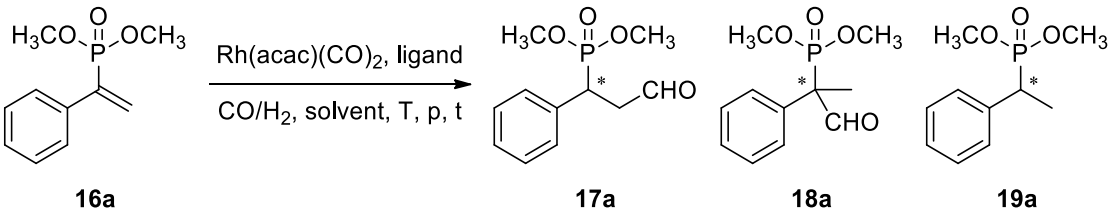
Furthermore, the phosphine oxide derivative **16i** was prepared from phenylacetylene and diphenylphosphine oxide in the presence of 5 mol% $Pd(OAc)_2$ and dppe (7 mol%). The reaction mixture was stirred at 100 °C for 14 h and the product could be obtained after column chromatography as a white solid in 73 % yield (Scheme 33).[104]



Scheme 33. Preparation of phosphine oxide **16i**: (*i*) 5 mol% $Pd(OAc)_2$, 7 mol% dppe, toluene, 100 °C, 14 h.

3.2.2.2 Initial asymmetric hydroformylation of dimethyl(1-phenylvinyl)phosphonate

We initiated our studies with non-asymmetric hydroformylation of dimethyl(1-phenylvinyl)phosphonate **16a** (Scheme 34). Next to both regioisomeric aldehydes, the hydrogenation product has to be taken into consideration, but no isomerization can occur. This minimizes the range of products and allows a greater variation of reaction conditions (Table 17).



Scheme 34. Hydroformylation of prochiral **16a**.

Table 17. Initial trials of the Rh-catalyzed non-asymmetric hydroformylation of **16a**.[a]

Entry	Ligand	*T* [°C]	*p* [MPa]	Conv.[b] [%]	17a[b] [%]	18a[b] [%]	19a[b] [%]
1	–	100	1.0	75	60	–	15
2[c]	Alkanox® 240	100	1.0	100	85	<1	15
3	BiPhePhos	100	1.0	93	83	<1	9
4	XantPhos	100	1.0	>99	90	1	9
5[c]	Alkanox® 240	100	2.0	95	78	3	14
6	BiPhePhos	100	2.0	>99	90	<1	9
7	XantPhos	80	2.0	68	58	3	7
8	XantPhos	80	1.0	91	81	2	8
9[d]	BiPhePhos	100	1.0	95	86	–	9
10[c]	Alkanox® 240	50	2.0	81	24	49	8
11	BiPhePhos	50	2.0	22	15	5	2

[a] 0.5 mmol of **16a**, $Rh(acac)(CO)_2$ 5.0 µmol, ligand 6.0 µmol, CO/H_2 = 1:1, 5 mL of toluene, *T*, *p*, S/Rh = 100, 21 h.
[b] Conversions and yields were determined by ^{31}P NMR spectroscopy.
[c] Ligand 15.0 µmol.
[d] Reaction was performed with a partial pressure ratio CO/H_2 = 2:1.

Firstly, it was tried to perform the hydroformylation with $Rh(acac)(CO)_2$ and without any organic ligand. Surprisingly, at 100 °C and syngas atmosphere (1 MPa), a reaction took place. After 21 h, the racemic linear aldehyde as well as the hydrogenation product could be determined with 60 % and 15 % yield, respectively (entry 1). By using the monodentate ligand Alkanox® 240, full conversion was reached with a better chemoselectivity toward the formation of the linear aldehyde (85 %), while the hydrogenation was still competitive under these conditions. Rhodium catalysts based on BiPhePhos and XantPhos diminished the degree of hydrogenation, while the conversion was kept at the same level (entries 3,4). Doubling the syngas pressure to 2 MPa in combination with a reaction temperature of 100 °C had no significant effect on the reactivity and yield of the desired product. When the ratio of the partial pressures of carbon monoxide to hydrogen was changed to 2:1, the results with BiPhePhos remained nearly the same (entry 9). The rate of the reaction faded enormously when the temperature was reduced to 50 °C (2 MPa syngas pressure, entry 11). At the same time, an increased amount of the branched aldehyde was noted (up to 49 %, entry 10).
Our work was continued with the asymmetric hydroformylation of the α-phosphorylated olefin **16a** (Table 18).

Table 18. Initial trials of the Rh-catalyzed asymmetric hydroformylation of **16a** with commercial ligands.[a]

Entry	Ligand	*T* [°C]	*p* [MPa]	Conv.[b] [%]	17a[b] [%]	18a[b] [%]	19a[b] [%]	ee[c] [%]
1	(*S*,*S*)-DIOP	100	1.0	95	86	7	2	9 (–)
2	(*R*,*R*)-DIPAMP	100	1.0	60	41	7	13	5 (–)
3	(*R*,*R*)-Me-DuPhos	100	1.0	58	35	6	16	1 (–)
4	(*S*,*S*)-BDPP	100	1.0	80	>33	>7	>14	21 (–)
5	(*R*)-MeO-BIPHEP	100	1.0	6	3	<1	2	n.d.
6	(*R*)-SynPhos	100	1.0	16	14	<1	2	rac
7	(*R*)-DifluorPhos	100	1.0	16	15	–	<1	rac
8	(*R*)-C_3-TunePhos	100	1.0	28	27	–	1	rac
9	(*R*)-4-Tol-BINAP	100	1.0	16	13	<1	2	2 (–)
10	(*R*,*R*)-QuinoxP*	100	1.0	98	35	7	56	21 (+)
11	(*S*,*S*)-BenzP*	100	1.0	98	17	7	74	21 (+)
12	(*R*,*R*,*S*)-BisDiazaPhos	100	1.0	98	83	11	5	3 (+)
13	(*R*,*R*)-Chiraphite	100	1.0	84	72	<1	11	2 (+)
14	(*R*,*R*)-Kelliphite	100	1.0	85	78	<1	6	rac
15	(*R*,*S*)-JosiPhos	100	1.0	23	12	2	9	16 (+)
16	(*S*,*S*)-BDPP	80	1.0	20	11	4	5	5 (–)
17	(*R*,*R*)-Chiraphite	80	1.0	43	37	<1	6	1 (+)
18	(*R*,*R*)-Kelliphite	80	1.0	77	71	<1	5	rac
19	(*R*,*R*)-Ph-BPE	80	1.0	45	2	29	14	37 (+)
20	(*S*,*S*)-DIOP	60	3.0	21	5	16	<1	13 (–)
21	(*S*,*S*)-BDPP	60	3.0	3	<1	2	<1	n.d.
22	(*R*,*R*,*S*)- Bisdiazaphos	60	3.0	7	3	3	1	13 (+)
23	(*R*,*R*)-Chiraphite	60	3.0	24	19	3	2	rac
24	(*R*,*R*)-Kelliphite	60	3.0	13	11	1	1	rac
25	(*R*,*R*)-Ph-BPE	60	3.0	4	–	4	<1	n.d.

[a] 0.5 mmol of **16a**, $Rh(acac)(CO)_2$ 5.0 µmol, PP-ligand 6.0 µmol, CO/H_2 = 1:1, 5 mL of toluene, *T*, *p*, S/Rh = 100, 21 h.
[b] Conversions and yields were determined by ^{31}P NMR spectroscopy.
[c] Ee-values of the linear aldehyde (**17a**) were determined by GC analysis.

Starting with (*S*,*S*)-DIOP, we promptly reached 95 % of conversion with a good chemo- and regioselectivity. Unfortunately, the resulting 86 % of the linear aldehyde were only of a low ee-value (entry 1). Trials with (*R*,*R*)-DIPAMP and (*R*,*R*)-Me-DuPhos did not succeed. In the runs at 100 °C and 1.0 MPa pressure of syngas atmosphere only low conversions were observed with low regioselectivity and a high amount of the hydrogenation product (entries 2,3). When the catalysis was examined with structurally similiar ligands like (*R*)-MeO-BIPHEP, (*R*)-SynPhos, (*R*)-DifluorPhos or (*R*)-C_3-TunePhos, no significant difference in the reactivity could be obtained (entries 5-8). The hydroformylation yielded low amounts of the aldehydes. In all cases, the ee-values were zero. Obviously, electronic differences within ligands do not play any role in the stereodifferentiation. Catalysts with *P*-chiral ligands (*R*,*R*)-QuinoxP* and (*S*,*S*)-BenzP* produced a huge amount of the hydrogenation product. The linear aldehyde arose with an ee-value of 21 % for both runs. Trials with the diphosphine ligand (*R*,*R*,*S*)-BisDiazaPhos as well as the chiral diphosphites (*R*,*R*)-Chiraphite and (*R*,*R*)-Kelliphite resulted either in a higher concentration of the branched aldehyde or of the hydrogenation product, but almost no stereodiscrimination was noted (entries 12-14). When the temperature was reduced to 80 °C, the reactivity of the catalyst decreased for all applied ligands. Surprisingly, the enantioselectivity dropped by application of (*S*,*S*)-BDPP, too (entry 16). Using (*R*,*R*)-Ph-BPE as ligand, the regioselectivity was reversed. 29 % yield of the branched aldehyde was formed compared to only 2 % of the linear one. With this ligand the highest ee-value of 37 % could be reached until then.

Further reduction of the temperature to 60 °C (and an increased syngas pressure to 3 MPa) resulted in poor or even no conversion. The increased amount of the branched aldehyde is also indicative and is in

accordance with the published results for other hydroformylations.[17a] With (*S*,*S*)-DIOP and (*R*,*R*,*S*)-BisDiazaPhos a slightly enhanced enantiomeric excess of the linear aldehyde can be registered. Due to the poor performance of the commercial ligands, we entered a project aimed to synthesize non-commercial as well as new ligands.

3.2.2.3 Synthesis of non-commercial and new ligands

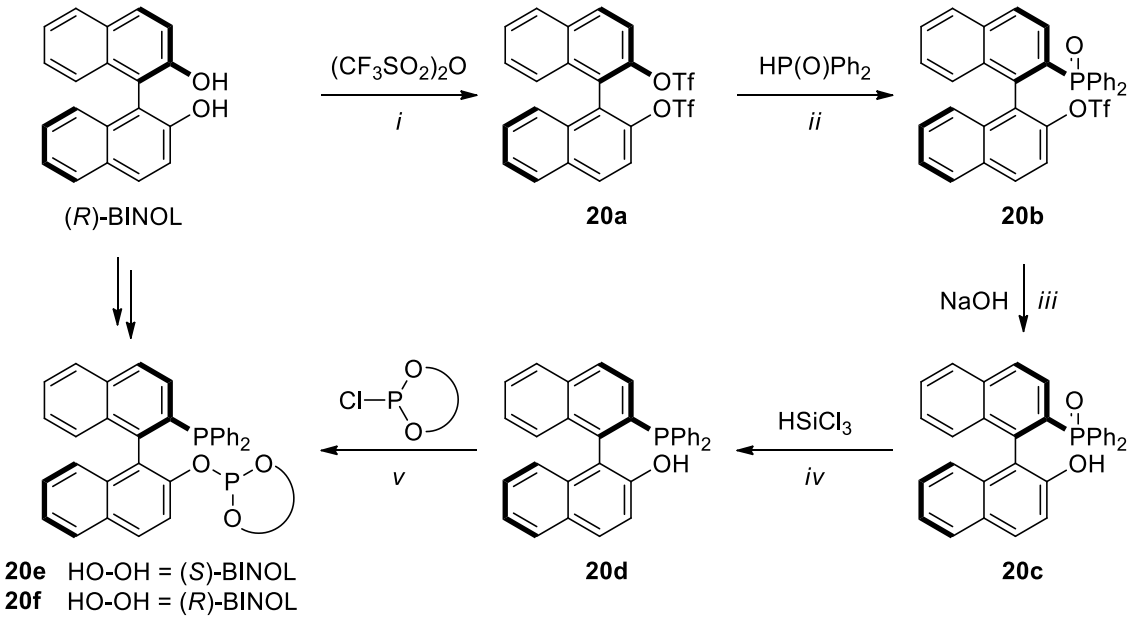
The number of commercially available bidentate ligands, which are successful candidates in asymmetric hydroformylation, is limited up to now. With the exception of some diphosphines only Chiraphite and Kelliphite represent chiral diphosphites that found application nowadays (see Chapter 2.3.2).

Since diastereomerically pure BINAPHOS is not supplied by fine chemical traders, we prepared it in a five-step synthesis[48,105] (Scheme 35). According to the procedure of Hayashi and co-workers[105] the hydroxyl groups of enantiomerically pure (*R*)-BINOL were transformed into triflate groups with trifluoroacetic anhydride in the presence of pyridine (pathway *i*). Resulting bistriflate **20a** was isolated as white solid in quantitative yield. Compound **20a** was then coupled with diphenylphosphine oxide[i] in the presence of $Pd(OAc)_2$ and dppb and in conjunction with an excess of Hünig's base. Monophosphine oxide **20b** could be isolated only in low yield (maximum 33 %, pathway *ii*).[ii] The other triflate group could be converted into a hydroxyl group by treatment with 3 M NaOH in dioxane/methanol at room temperature for 16 h. Phosphine oxide **20c** was isolated in almost quantitative yield as a white solid (pathway *iii*). The phosphine oxide was reduced to a phosphine (**20d**) by treatment with an excess of trichlorosilane and triethylamine at 100 °C in toluene for 16 h. The phosphine yielded in 82 % as a white solid (pathway *iv*). This compound was reacted with either the chlorophosphite of (*S*)-BINOL or (*R*)-BINOL[iii] and a slight excess of triethylamine. The products, (*R*,*S*)-BINAPHOS (47 %, **20e**) and (*R*,*R*)-BINAPHOS (40 %, **20f**), emerged as white solids after column chromatography over alumina (pathway *v*) as described by Takaya.[48]

[i] Diphenylphosphine oxide was prepared by stirring chloro diphenylphosphine in 1 M HCl and isolated as a white solid in 98 % yield.[106]

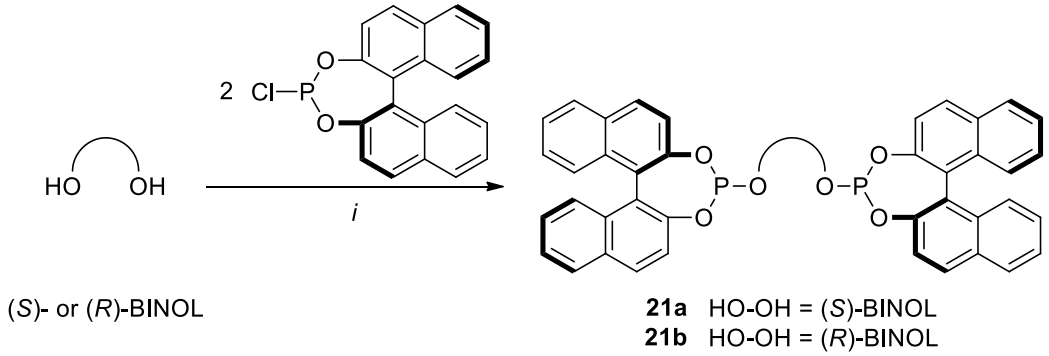
[ii] The reaction was repeated a few times with different batches of the starting material. For instance, diphenylphosphine oxide from SIGMA ALDRICH® as well as Pd(OAc) from different suppliers were used, but did not lead to any improvement of the yield.

[iii] To prepare the chlorophosphite of enantiopure BINOL *in situ* the diol was suspended in phosphorus trichloride, 2-3 drops of NMP were added and the suspension was heated to 75 °C for 5 min until it became clear. Evaporation yielded the desired chlorophosphite as a pale yellow solid.[107]



Scheme 35. Synthesis of (*R*,*S*)- and (*R*,*R*)-BINAPHOS (**20e** and **20f**): (*i*) 3.5 eq pyridine, DCM, 0 °C → r.t., 6 h; (*ii*) 5 mol% $Pd(OAc)_2$, 5 mol% dppb, 4.0 eq Hünig's base, DMSO, 100 °C, 20 h; (*iii*) dioxane/methanol (*v*:*v* 1:1), r.t., 16 h; (*iv*) 7.2 eq Et_3N, toluene, 100 °C, 16 h; (*v*) 2.5 eq Et_3N, toluene, 0 °C → r.t., 16 h.

In addition, some chiral diphosphite ligands could be prepared based on different aromatic diols. (*S*)- and (*R*)-BINOL, respectively, was coupled with the chlorophosphites of (*R*)-BINOL (2.1 eq) when the reaction was stirred at room temperature for 16 h in the presence of an excess of triethylamine. The (*R*,*S*,*R*)- and (*R*,*R*,*R*)-diphosphite were isolated as white solids in 95 % (**21a**) and 93 % (**21b**) after column chromatography over alumina (Scheme 36).

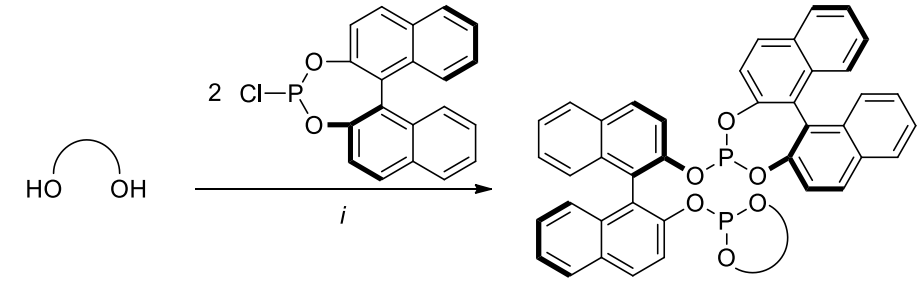


Scheme 36. Synthesis of diphosphite ligands **21a,b**: (*i*) 5.0 eq Et_3N, toluene, 0 °C → r.t., 16 h.

When achiral 4,4',6,6'-tetra-*tert*-butyl-2,2'-biphenol[i] and 4,4'-di-methoxy-6,6'-di-*tert*-butyl-2,2'-biphenol[ii] were employed as backbones to the reaction, non-symmetric diphosphites were obtained. The reaction with the chlorophosphite of (*R*)-BINOL yielded **21c** and **21d**, respectively, under the same conditions as for the prior synthesized diphosphite ligands **21a,b**. Compounds **21c** and **21d** showed unexpected two signals in a relation of 1:1 in the ^{31}P NMR, what means that they do not have chemical equivalent phosphorus atoms and, consequently, transesterfication might has taken place (Scheme 37).[110] Both compounds could be isolated as white solids after column chromatography over alumina in 94 % (**21c**) and 97 % (**21d**) yield, respectively.

[i] 4,4',6,6'-Tetra-*tert*-butyl-2,2'-biphenol was prepared from 2,4-di-*tert*-butylphenol and MnO_2 in heptane. Stirring under reflux for 3.5 h yielded an off-white solid in 85 %.[108]

[ii] 4,4'-Di-methoxy-6,6'-di-*tert*-butyl-2,2'-biphenol was prepared from 3-*tert*-butyl-4-hydroxyanisole, KOH and $K_3[Fe(CN)_6]$ in methanol. Strirring at room temprature for 5 h yielded an off-white solid in 98 %.[109]

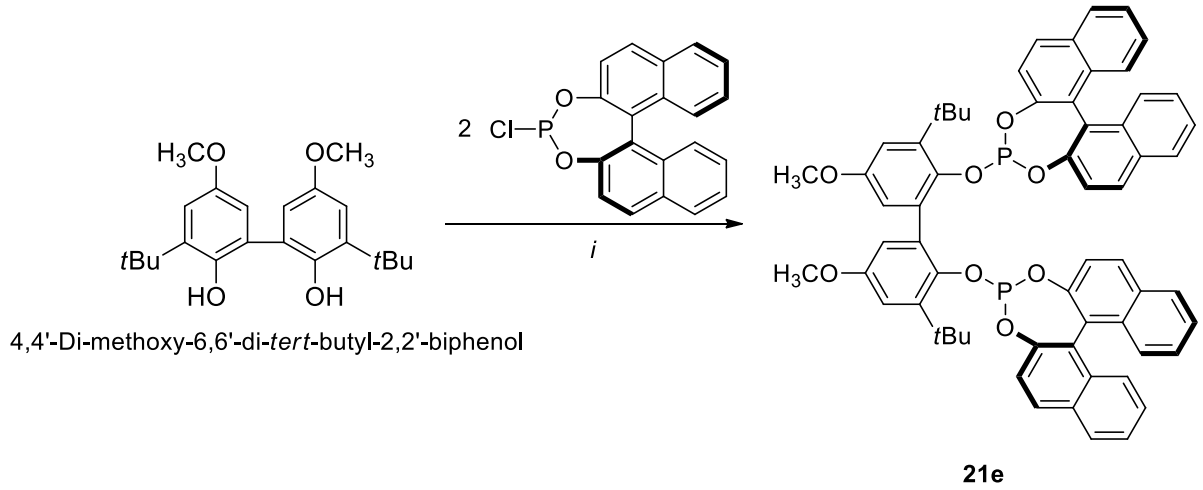


Aromatic diols

21c HO-OH = 4,4',6,6'-Tetra-*tert*-butyl-2,2'-biphenol
21d HO-OH = 4,4'-Di-methoxy-6,6'-di-*tert*-butyl-2,2'-biphenol

Scheme 37. Synthesis of diphosphite ligands **21c,d**: (*i*) 5.0 eq Et_3N, toluene, 0 °C → r.t., 16 h.

When 4,4'-di-methoxy-6,6'-di-*tert*-butyl-2,2'-biphenol was reacted with the chlorophosphite of (*R*)-BINOL in the presence of *n*-BuLi at -20 °C, symmetric diphosphite ligand **21e** yielded in 61 % as a white solid (Scheme 38).



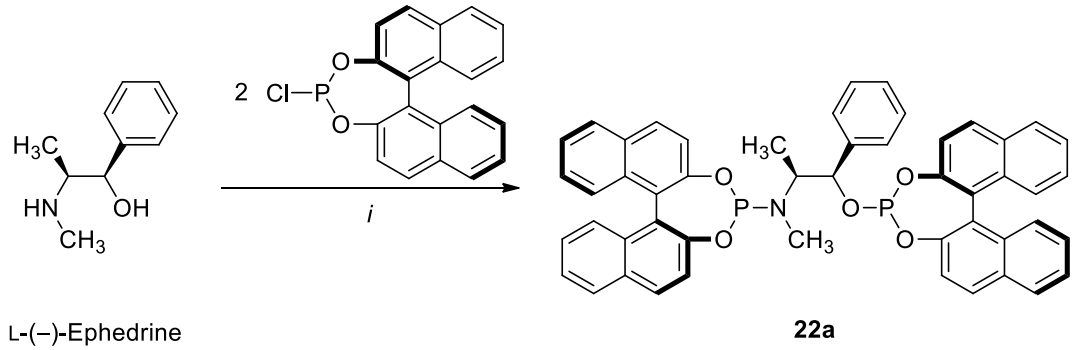
4,4'-Di-methoxy-6,6'-di-*tert*-butyl-2,2'-biphenol

21e

Scheme 38. Synthesis of diphosphite ligand **21e**: (*i*) 1.0 eq *n*-BuLi, toluene, -20 °C → r.t., 16 h.

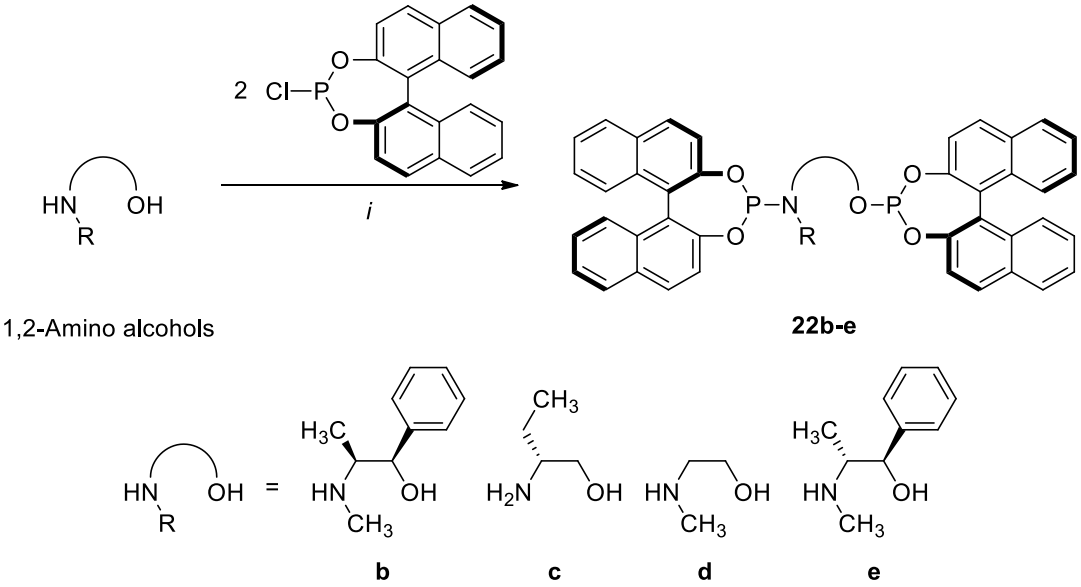
Furthermore, new bidentate chiral phosphite-phosphoramidite ligands were prepared on the basis of readily accessible amino alcohols and chiral as well as non-chiral diols.

Although L-(–)-ephedrine was already suggested as a backbone for phosphite-phosphoramidite ligands in the literature,[111] they have never been synthesized in combination with enantiomerically pure BINOL. We used it as starting material for the construction of phosphite-phosphoramidite **22a**. It was reacted with 2.1 eq of the chlorophosphite of (*S*)-BINOL and 5.0 eq of triethylamine. Stirring at room temperature for 16 h yielded **22a** as a white solid after column chromatography over alumina (52 %, Scheme 39).



Scheme 39. Synthesis of phosphite-phosphoramidite **22a** with (*S*)-BINOL based on L-(–)-ephedrine: (*i*) 5.0 eq Et_3N, toluene, 0 °C → r.t., 16 h.

According to this procedure L-(–)-ephedrine was also treated with the chlorophosphite of (*R*)-BINOL to yield **22b** as a white solid (65 %). Because the ligands, derived from (*R*)-BINOL, were especially promising for the asymmetric hydroformylation of **16a** (see Chapter 3.2.2.4), other 1,2-amino alcohols were taken into consideration (Scheme 40).



Scheme 40. Synthesis of phosphite-phosphoramidites **22b-e** with (*R*)-BINOL based on different 1,2-amino alcohols: (*i*) 5.0 eq Et_3N, toluene, 0 °C → r.t., 16 h.

In conclusion, five new phosphite-phosphoramidite compounds **22a-e** could be prepared with yields of 28-81% (Table 19).

Table 19. Synthesis of phosphite-phosphoramidites **22a-e** based on different 1,2-amino alcohols.[a]

Entry	Amino alcohol	R^1	R^2	R^3	BINOL	Product	Yield[b] [%]
1	L-(–)-Ephedrine	Me	Me	Ph	(*S*)-BINOL	**22a**	52
2					(*R*)-BINOL	**22b**	65
3	(*R*)-2-Aminobutan-1-ol	H	Et	H	(*R*)-BINOL	**22c**	28
4	2-(Methylamino)ethanol	Me	H	H	(*R*)-BINOL	**22d**	36
5	(–)-Pseudoephedrine	Me	Me	Ph	(*R*)-BINOL	**22e**	81

[a] 1.0 mmol of 1,2-amino alcohol, 2.1 mmol of chlorophosphite of enantiopure BINOL, 5.0 mmol Et_3N, toluene, 0 °C → r.t., 16 h.
[b] Isolated yields after column chromatography over alumina.

Amino sugar-based bidentate ligands have been prepared by Diéguez and co-workers recently.[112] All of them have in common that a hydrogen is linked to the nitrogen atom (secondary amine). For this

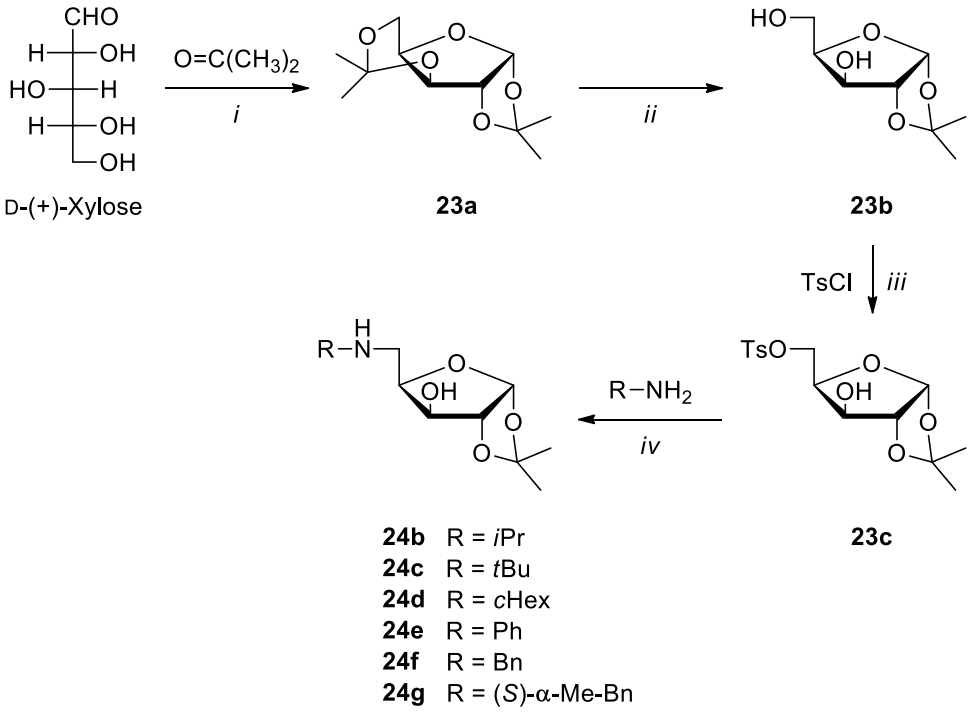
reason, we focused on the synthesis of *N*-alkylated phosphite-phosphoramidites based on 1,2-*O*-diprotected α-D-xylofuranose. α-D-Ribofuranose as backbone faded away from our spotlight due to the poor performance in the asymmetric hydroformylation of **16a** (see Chapter 3.2.2.4).

Starting from open-chain D-(+)-xylose, the hydroxyl groups were protected by isopropylidene groups according to the procedure of Kartha.[113] Therefore, the sugar was dissolved in acetone and a small portion of iodine was added as an activator. Stirring at room temperature for 16 h and common aqueous work-up gave 96 % of protected α-D-xylofuranose **23a** as a yellowish solid (pathway *i*, Scheme 41). In this compound, the original hydroxyl groups are protected by differently sized 1,3-dioxo rings. Because a six-membered 2,2-dimethyl-1,3-dioxane is less stable than a five-membered 2,2-dimethyl-1,3-dioxolane toward acidic conditions,[114] selective deprotection is possible.[i] The acetal, involving C-3 and C-5, could be cleaved when **23a** was stirred in an aqueous solution of sulphuric acid at room temperature for 16 h. Neutralization and filtration over Celite yielded 1,2-*O*-diprotected α-D-xylofuranose **23b** as a yellowish viscous oil (92 %, pathway *ii*).[115] Subsequent transformation of the hydroxyl group at C-5 into a leaving group (tosylate) was realized when **23b** was stirred with tosyl chloride in pyridine at room temperature for 16 h. After aqueous work-up a mixture of mono- und ditosylated crude product could be obtained, what was separated by recrystallization. At -20 °C the monotosylated compound **23c** precipitated and could be isolated as a white solid in 60 % yield after filtration (pathway *iii*).[116],[ii]

The amino xylose derivatives **24b-g** were prepared from protected 5-tosyl-α-D-xylofuranose **23c** and a variety of primary amines. A S_N2-reaction occurs at C-5 that is attacked by the nucleophilic amine. The reaction was either performed without a solvent at 60 °C (for **24b**)[117] or in isopropanol under reflux (for **24c-g**).[118] Aqueous work-up (except for **24b**) and column chromatography yielded **24b-g** as yellowish solids (pathway *iv*). The yields are given in Table 20. Product **24g** was synthesized and characterized for the first time.

[i] "Orthogonality" or "orthogonal protection" is a strategy for the deprotection of functional groups independendly of each other.

[ii] A large quantity of **23c** was provided by the research group of Prof. Diéguez at Universitat Rovira í Virgili in Tarragona/Spain.



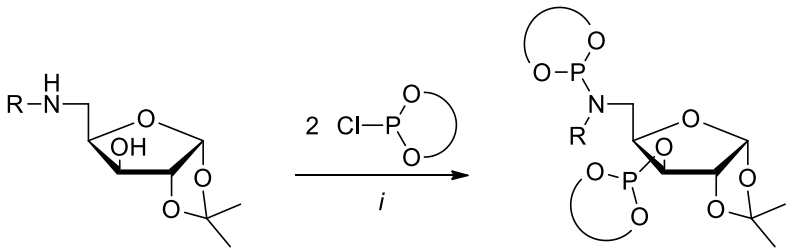
Scheme 41. Synthesis of amino xylose derivatives **24b-g**: (*i*) I_2, r.t., 16 h; (*ii*) 0.8 % H_2SO_4, MeOH, r.t., 16 h; (*iii*) pyridine, DCM, 0 °C → r.t., 16 h; (*iv*) neat, 60 °C, 24 h *or* isopropanol, reflux, 24 h.

Table 20. Synthesis of amino xylose derivatitives **24b-g** based on xylose derivative **23c**.[a]

Entry	Amine	R	Product	Yield[b] [%]
1[c]	Isopropylamine	*i*Pr	**24b**	61
2	*tert*-Butylamine	*t*Bu	**24c**	41
3	Cyclohexylamine	*c*Hex	**24d**	63
4	Aniline	Ph	**24e**	86
5	Benzylamine	Bn	**24f**	61
6	(*S*)-α-Methyl-benzylamine	(*S*)-α-Me-Bn	**24g**	99

[a] 10.0-15.0 mmol of **23c**, 40.0-60.0 mmol of amine, isopropanol, 60 °C, 24 h.
[b] Isolated yields after column chromatography over silica.
[c] A large excess of amine was used instead of a solvent. Reaction was performed under reflux.

Amino xylose derivatives **24b-g** served as starting material for a range of new bidentate phosphite-phosphoramidite ligands. According to the procedure of Diéguez *et al.*[112a,b] it was first tried to couple the *N*- as well as *O*-moiety, simultaneously, with the chlorophosphite of enantiopure BINOL using pyridine as a base. Starting from **24b**, 12 eq of pyridine and 2.2 eq of the chlorophosphite of (*S*)-BINOL, only the signal for the chlorophosphite could be detected in ^{31}P NMR after stirring at room temperature for 16 h. Therefore, the solution was heated to 100 °C and stirred for the same time again. In ^{31}P NMR a signal at δ = 145.3 ppm appeared, what was assigned to the *O*-phosphorylated product. Based on these results it can be concluded that the alkylated *N*-moiety of the amino xylose is not acidic enough to be deprotonated by pyridine, even at higher temperature. Consequently, it required a change to a stronger base, e.g. triethylamine. Amino alcohol **24b** was reacted with the (*S*)-BINOL chlorophosphite in the presence of 5 eq of triethylamine at room temperature for 16 h. After column chromatography over basic silica, phosphite-phosphoramidite **25b** could be isolated as a white solid (35 %). The ^{31}P NMR spectrum was characterized by a doublet at δ = 151.4 ppm and a doublet at δ = 153.3 ppm for the phosphite- and phosphoramidite-*P*.
Increasing the reaction temperature to 50 °C, the yield of **25b** could be raised to 76 %. With this improvement, 12 new phosphite-phosphoramidites (**25a-g** and **26b,d-g**) were synthesized with yields up to 97 % (Scheme 42, Table 21).



24a R = Me
24b R = *i*Pr
24c R = *t*Bu
24d R = *c*Hex
24e R = Ph
24f R = Bn
24g R = (*S*)-α-Me-Bn

25a R = Me, HO-OH = (*S*)-BINOL
25b R = *i*Pr, HO-OH = (*S*)-BINOL
25c R = *t*Bu, HO-OH = (*S*)-BINOL
25d R = *c*Hex, HO-OH = (*S*)-BINOL
25e R = Ph, HO-OH = (*S*)-BINOL
25f R = Bn, HO-OH = (*S*)-BINOL
25g R = (*S*)-α-Me-Bn, HO-OH = (*S*)-BINOL
26b R = *i*Pr, HO-OH = (*R*)-BINOL
26d R = *c*Hex, HO-OH = (*R*)-BINOL
26e R = Ph, HO-OH = (*R*)-BINOL
26f R = Bn, HO-OH = (*R*)-BINOL
26g R = (*S*)-α-Me-Bn, HO-OH = (*R*)-BINOL

Scheme 42. Synthesis of xylose-based phospite-phosphoramidites **25a-g** and **26b,d-g**: (*i*) 5.0 eq Et_3N, toluene, 0 °C → 50 °C, 16 h.

Table 21. Synthesis of phosphite-phosphoramidites **25a-g** and **26b,d-g** based on amino xylose derivatives **24a-g**.[a,i]

Entry	Amino xylose	R	BINOL	Product	Yield[b] [%]
1	**24a**	Me	(*S*)-BINOL	**25a**	85
2[c]	**24b**	*i*Pr	(*S*)-BINOL	**25b**	35
3			(*S*)-BINOL	**25b**	76
4			(*R*)-BINOL	**26b**	90
5	**24c**	*t*Bu	(*S*)-BINOL	**25c**	29
6	**24d**	*c*Hex	(*S*)-BINOL	**25d**	97
7			(*R*)-BINOL	**26d**	97
8	**24e**	Ph	(*S*)-BINOL	**25e**	33
9			(*R*)-BINOL	**26e**	33
10	**24f**	Bn	(*S*)-BINOL	**25f**	81
11			(*R*)-BINOL	**26f**	85
12	**24g**	(*S*)-α-Me-Bn	(*S*)-BINOL	**25g**	89
13			(*R*)-BINOL	**26g**	62

[a] 1.0 mmol of **24a-g**, 2.2 mmol of chlorophosphite of enantiopure BINOL, 5.0 mmol Et_3N, toluene, 0 °C → 50 °C, 16 h.
[b] Isolated yields after column chromatography over basic silica.
[c] The reaction was stirred at room temperature for 16 h.

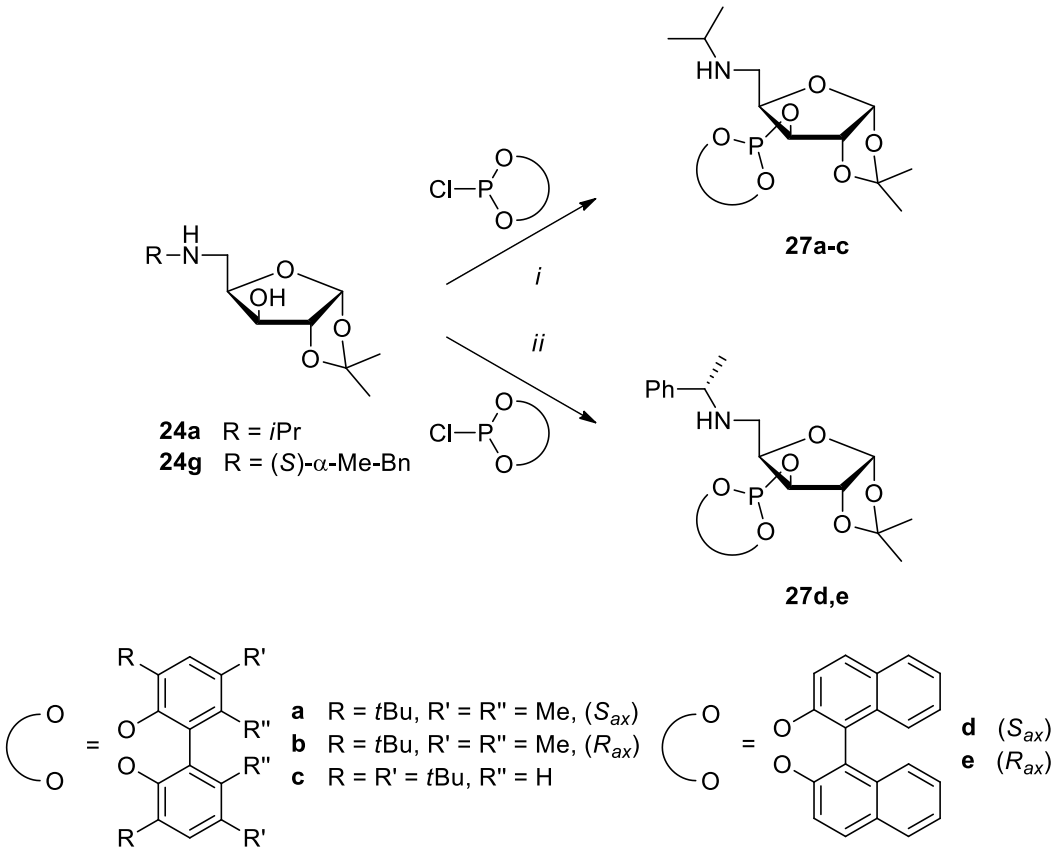
Additionally, phosphite-phosphoramidites with non-equal substituents at both phosphorus atoms were prepared based on amino xyloses **24b,g**. Introducing two different groups makes a reaction over two steps necessary. At first, the monophosphite was prepared followed by the coupling of the second chlorophosphite to the *N*-moiety.

Starting from amino xylose **24b**, 4.6 eq of pyridine and 1.1 eq of the chlorophosphite of (*S*)-BIPHEN-H_2[ii] in toluene, the reaction was stirred at 80 °C for 16 h. Column chromatography over silica with 2 % of triethylamine in toluene yielded 85 % of a white solid. The added base is necessary, inter alia, to ensure that the generated ammonium group of the xylose is retransformed into an amino

[i] Amino-xylose **24a** was provided by the research group of Prof. Diéguez at Universitat Rovira í Virgili in Tarragona/Spain.
[ii] To prepare the chlorophosphite of enantiopure BIPHEN-H_2 or bisDBP, respectively, *in situ*, the aromatic diol was dissolved in toluene, an excess of pyridine was added and the solution was stirred for 16 h at 80 °C. Filtration from the pyridinium salt, followed by evaporation of the solvent yielded the desired chlorophosphite as a pale yellow solid.

group.[i] One can assume that pyridine is less basic than the amino group of the sugar so that the *N*-moiety of the xylose is preferentially protonated during the reaction. To isolate phosphite **27a**, instead of its ammonium salt, a stronger base than pyridine is needed for the deprotonation. According to this procedure three new monophosphites **27a-c**[ii] were prepared as white solids in 62-85 % yield (Table 22, entries 1-3).

With amino sugar **24g**, monophosphites **27d,e** could only be isolated as crude ammonium salts (Table 22, entries 4,5). Purification by recrystallization as well as column chromatography (with additional Et_3N) failed. For that reason they were directly used for further reactions.



Scheme 43. Synthesis of xylose-based monophosphites **27a-c** and **27d,e**: (*i*) 4.6 eq pyridine, toluene, 0 °C → 80 °C, 16 h.

Table 22. Synthesis of monophosphites **27a-e** based on amino xylose derivatives **24a,g**.[a]

Entry	Amino xylose	R	Aromatic diol	Product	Yield[b] [%]
1	**24a**	*i*Pr	(*S*)-BIPHEN-H_2	**27a**	85
2			(*R*)-BIPHEN-H_2	**27b**	76
3			bisDBP	**27c**	62
4	**24g**	(*S*)-α-Me-Bn	(*S*)-BINOL	**27d**	99[c]
5			(*R*)-BINOL	**27e**	98[c]

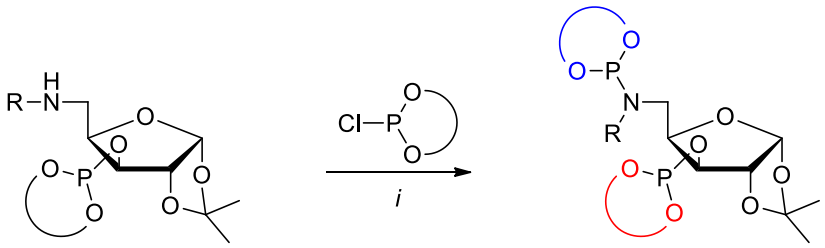
[a] 2.0 mmol of **24a,g**, 2.2 mmol of chlorophosphite of (enantiopure) aromatic diol, 4.6 mmol pyridine, toluene, r.t. → 80 °C, 16 h.
[b] Isolated yields after column chromatography over alumina.
[c] The crude product of the ammonium salt was isolated without further purification.

Monophosphites **27a-e** were used as starting material for the synthesis of mixed phosphite-phosphoramidites. Corresponding to the preparation of phosphite-phosphoramidites **25a-g** and

[i] The pyridine keeps the reaction medium basic and works partly as a proton sponge, too.
[ii] The three monophosphite ligands **27a-c** were synthesized in cooperation with Marc Magre Rosich from research group of Prof. Diéguez at Universitat Rovira í Virgili in Tarragona/Spain.

26b,d-g, respectively (see above), the reaction was performed with 5.0 eq of triethylamine and 1.1 eq of the chlorophosphite of enantiopure BINOL. Stirring at 50 °C for 16 h yielded **28a-f** as white solids (starting from **27a-c**) after column chromatography over silica.

To prepare phosphite-phosphoramidite xyloses with varying BINOL units at the phosphorus of the *O*-side and different diols at the phosphorus of the *N*-moiety, crude products **27d,e** were treated with 2.0 eq of triethylamine and stirred at 50 °C for 16 h. Precipitated ammonium chloride could be removed by filtration. The ^{1}H NMR spectrum of the crude material reveals that both singlets at $\delta = 11.01$ ppm and 11.40 ppm disappeared and thus an evidence for the free amino function. Purification by recrystallization or by column chromatography failed so that they were directly converted into the corresponding phosphite-phosphoramidites **28g-i** (see above, Scheme 44, Table 23).



27a R = *i*Pr, HO-OH = (*S*)-BIPHEN-H$_2$
27b R = *i*Pr, HO-OH = (*R*)-BIPHEN-H$_2$
27c R = *i*Pr, HO-OH = bisBDP
27d R = (*S*)-α-Me-Bn, HO-OH = (*S*)-BINOL
27e R = (*S*)-α-Me-Bn, HO-OH = (*R*)-BINOL

28a R = *i*Pr, HO-OH = (*S*)-BIPHEN-H$_2$
HO-OH = (*S*)-BINOL
28b R = *i*Pr, HO-OH = (*S*)-BIPHEN-H$_2$
HO-OH = (*R*)-BINOL
28c R = *i*Pr, HO-OH = (*R*)-BIPHEN-H$_2$
HO-OH = (*S*)-BINOL
28d R = *i*Pr, HO-OH = (*R*)-BIPHEN-H$_2$
HO-OH = (*R*)-BINOL
28e R = *i*Pr, HO-OH = bisBDP
HO-OH = (*S*)-BINOL
28f R = *i*Pr, HO-OH = bisBDP
HO-OH = (*R*)-BINOL
28g R = (*S*)-α-Me-Bn, HO-OH = (*S*)-BINOL
HO-OH = (*R*)-BINOL
28h R = (*S*)-α-Me-Bn, HO-OH = (*S*)-BINOL
HO-OH = bisBDP
28i R = (*S*)-α-Me-Bn, HO-OH = (*R*)-BINOL
HO-OH = (*S*)-BINOL

Scheme 44. Synthesis of xylose-based mixed phosphite-phosphoramidites **28a-i**: (*i*) 4.0 eq Et_3N, toluene, 0 °C → 50 °C, 16 h.

Table 23. Synthesis of mixed phosphite-phosphoamidites **28a-i** based on monophosphites **27a-e**.[a]

Entry	Monophosphite	R	Aromatic diol	Product	Yield[b] [%]
1	**27a**	(*S*)-BIPHEN-H_2	(*S*)-BINOL	**28a**	43
2			(*R*)-BINOL	**28b**	76
3	**27b**	(*R*)-BIPHEN-H_2	(*S*)-BINOL	**28c**	62
4			(*R*)-BINOL	**28d**	73
5	**27c**	bisDBP	(*S*)-BINOL	**28e**	71
6			(*R*)-BINOL	**28f**	89
7	**27d**	(*S*)-BINOL	(*R*)-BINOL	**28g**	35[c]
8			bisDBP	**28h**	24[c]
9	**27e**	(*R*)-BINOL	(*S*)-BINOL	**28i**	21[c]
10			bisDBP	**28j**	–[c]

[a] 0.33-0.5 mmol of **27a-e**, 0.36-0.55 mmol of chlorophosphite of (enantiopure) aromatic diol, 1.6-2.6 mmol Et_3N, toluene, 0 °C → 50 °C, 16 h.
[b] Isolated yields after column chromatography over basic silica.
[c] Isolated yield over two steps after column chromatography over basic silica.

3.2.2.4 Asymmetric hydroformylation with non-commercial and new ligands

After widening the set of ligands, we continued the hydroformylation trials of **16a**. All conditions remained the same as chosen for the preliminary attempts of asymmetric hydroformylation discussed above (see Chapter 3.2.2.2).
At first, (*R*,*S*)- and (*R*,*R*)-BINAPHOS (**20e** and **20f**) and the ligands, derived from 1,2-amino alcohols, were tested (Table 24).

Table 24. Screening of the Rh-catalyzed asymmetric hydroformylation of **16a** with self-prepared phosphorus ligands.[a]

Entry	Ligand	*p* [MPa]	Conv.[b] [%]	17a[b] [%]	18a[b] [%]	19a[b] [%]	ee[c] [%]
1	**20e**	1.0	57	51	3	3	41 (+)
2	**20f**	1.0	42	39	1	2	3 (–)
3	**22a**	1.0	69	64	1	4	23 (–)
4	**22b**	1.0	99	96	1	1	46 (+)
5	**22c**	1.0	69	64	1	5	24 (+)
6	**22d**	1.0	63	59	1	3	26 (+)
7	**22e**	1.0	97	93	2	2	24 (+)
8[d]	**22b**	1.0	63	60	1	2	34 (+)
9[e]	**22b**	1.0	31	28	1	2	43 (+)
10	**22b**	0.5	99	96	<1	3	44 (+)
11	**22b**	5.0	67	52	13	2	32 (+)
12[f]	**22b**	3.0	36	25	11	<1	51 (+)
13[g]	**22b**	1.0	11	6	5	<1	47 (+)

[a] 0.5 mmol of **16a**, $Rh(acac)(CO)_2$ 5.0 µmol, PP-ligand 6.0 µmol, CO/H_2 = 1:1, 5 mL of toluene, 80 °C, *p*, S/Rh = 100, 21 h.
[b] Conversions and yields were determined by ^{31}P NMR spectroscopy.
[c] Ee-values of the linear aldehyde (**17a**) were determined by GC analysis.
[d] The reaction was performed in EtOAc.
[e] The reaction was performed in DCM.
[f] The reaction was performed at 60 °C.
[g] The reaction was performed at room temperature for 63 h.

The rhodium-catalyzed reaction with (*R*,*S*)-BINAPHOS (**20e**) revealed only a mediocre enantioselectivity (41 %ee) with a poor conversion rate (entry 1). Diastereomeric (*R*,*R*)-BINAPHOS **20f** showed even worse results in both aspects (entry 2).
The reaction with **22a** gave only a moderate conversion (69 %) with low enantioselectivity of 23 %ee. However, the rhodium catalyst with L-(–)-ephedrine-based phosphite-phosphoramidite **22b** showed first promising results. The highest ee-value of 46 %, quantitative conversion and excellent selectivity to the linear aldehyde could be reached for the first time (entry 3). Encouraged by this result,

structurally related ligands **22c-e**, bearing (*R*)-BINOL, were employed. They induced good to very good chemo- and regioselectivities to the linear aldehyde on the one hand, but the enantioselectivities were still poor (entries 5-7). A comparison of the results of ligands **22b** and **22e** shows that a change of the configuration at carbon C-1 (L-(–)-ephedrine and (–)-pseudoephedrine) affected the enantioselectivity. Furthermore, the hydroformylation, using **22b**, was also performed in EtOAc and DCM, but led to no improvement (entries 8,9). Therefore, we switched back to toluene as solvent and ran the asymmetric hydroformylation at different pressures. At a syngas pressure of 0.5 MPa, no changes of reactivity as well as enantioselectivity could be noted (entry 10). A higher pressure had a negative influence (entry 11). A lower temperature had a slightly positive effect on the stereodiscrimination, but the reactivity decreased, simultaneously (entries 12,13).
During these screenings it was also possible to perform the asymmetric hydroformylation of **16a** in the research group of Prof. Diéguez (Table 25). The provided set of sugar-based ligands is illustrated in Figure 17.

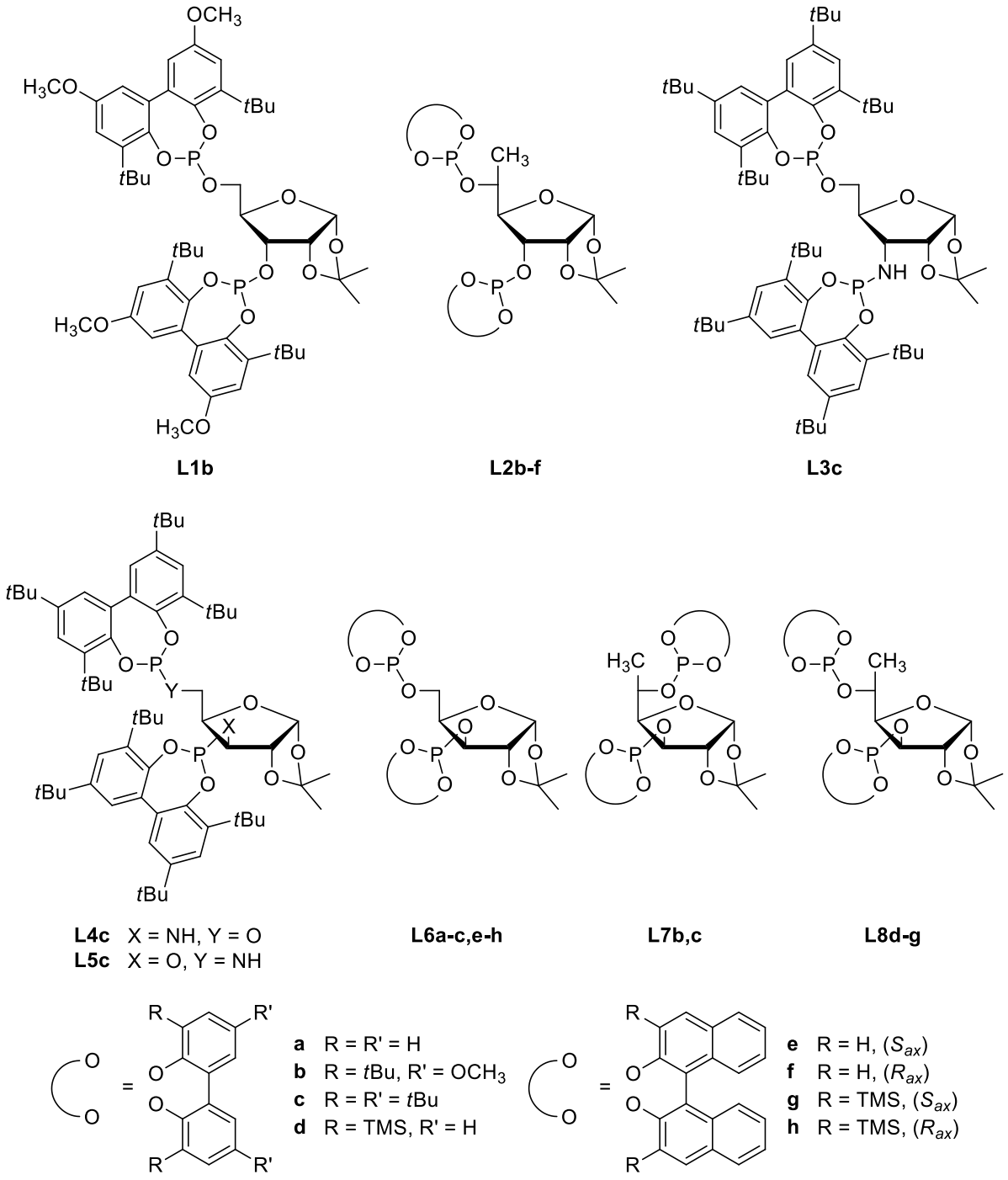


Figure 17. Provided set of sugar-based ligands used in the asymmetric hydroformylation of **16a**.

Table 25. Screening of the Rh-catalyzed asymmetric hydroformylation of **16a** with sugar-based phosphorus ligands **L1-8**.[a]

Entry	Ligand	Conv.[b] [%]	17a[b] [%]	18a[b] [%]	19a[b] [%]	ee[c] [%]
1	**L1b**	33	27	1	5	1 (+)
2	**L2b**	70	63	2	5	rac
3	**L2c**	18	15	2	2	17 (+)
4	**L2d**	100	81	<1	19	rac
5	**L2e**	100	98	<1	2	37 (–)
6	**L2f**	100	98	<1	1	30 (+)
7	**L3c**	85	58	–	27	2 (+)
8	**L4c**	81	68	–	13	5 (–)
9	**L5c**	76	54	–	22	2 (+)
10	**L6a**	>99	96	<1	3	7 (–)
11	**L6b**	59	52	1	6	rac
12	**L6c**	52	45	1	6	rac
13	**L6e**	100	>99	<1	1	46 (–)
14	**L6f**	100	98	<1	2	9 (–)
15	**L6g**	66	51	<1	14	4 (+)
16	**L6h**	100	81	–	19	3 (+)
17	**L7b**	48	40	4	4	6 (+)
18	**L7c**	49	40	5	4	14 (+)
19	**L8d**	2	1	–	<1	n.d.
20	**L8e**	77	74	<1	3	4 (+)
21	**L8f**	100	96	<1	4	11 (–)
22	**L8g**	3	2	–	1	25 (+)
23[d]	**L6e**	85	82	3	<1	51 (–)
24[e]	**L6e**	24	21	2	–	56 (–)
25[e]	**L2e**	35	33	1	<1	45 (–)

[a] 0.5 mmol of **16a**, $Rh(acac)(CO)_2$ 5.0 µmol, PP-ligand 6.0 µmol, CO/H_2 = 1:1, 5 mL of toluene, 80 °C, 1.0 MPa, S/Rh = 100, 21 h.
[b] Conversions and yields were determined by ^{31}P NMR spectroscopy.
[c] Ee-values of the linear aldehyde (**17a**) were determined by GC analysis.
[d] The reaction was performed at 60 °C.
[e] The reaction was performed at 40 °C.

The asymmetric hydroformylation was first started with the diphosphite ligand **L1b**, based on α-D-ribofuranose, what bears a non-chiral biphenol at both phosphorus atoms.[i] An almost racemic mixture of the linear aldehyde with a comparatively high amount of hydrogenation product could be obtained and, furthermore, the conversion was low (33 %). To see any influence of an additional stereogenic center at the C-5 carbon ligands of type **L2** were employed to the reaction. The α-D-allofuranose-based ligands showed either modest to poor conversion rates (entries 2,3) or disappointing chemoselectivity (entry 4). In all cases, the ee-values were pretty low. However, trials performed with **L2e** and **L2f**, respectively, showed excellent yields of the linear aldehyde and moreover promising ee's.

When phosphite-phosphoramidite ligands **L3c**, **L4c** and **L5c** (with an opposing chirality at C-3) were used, low ee-values yielded. Moreover, hydrogenation became a strong competitive reaction (entries 7-9).

Changing to α-D-xylofuranose-based ligands **L6** resulted in excellent conversion for some trials (entries 10,13,14,16), but ee-values still remained low except for ligand **L6e**. Highest chemo-, regio- and stereoselectivity (46 %ee) could be observed. Surprisingly, when ligands **L6g,h** were applied, having TMS-groups at the 3,3'-positions of the BINOLs, the enantioselectivity was affected. Additionally, it promoted the hydrogenation (entries 15,16). Structurally related ligands **L7** and **L8**

[i] However, due to the chirality of the sugar backbone, it can be assumed that, especially in the metal-complexes, a certain configuration is preferred. This effect of tropos ligands, becoming atropos, has been observed for example with chiral Ru-diamine-complexes bearing 2,2'-biphenyl diphosphines as a counter-ligand.[119]

gave only small to moderate conversions (except for **L8f**). The additional methyl group at C-5, independently on the carbon atom configuration, seems to have a negative influence on the enantioselectivities of **17a** (entries 17-22).
At last, further trials with ligands **L2e** and **L6e** at lower temperatures (60 °C and 40 °C) were performed and showed best ee-values. The enantioselectivities slightly increased from 46 %ee to 56 %ee and from 37 %ee to 45 %ee, respectively. Certainly, the conversion rates stagnated, but no loss of chemo- and regioselectivity could be determined (entries 23-25).
Based on the promising results achieved with **L6e**, structurally related phosphite-phosphoramidites were synthesized (see Chapter 3.2.2.3) and tested for the asymmetric hydroformylation of **16a** (Table 26).

Table 26. Screening of the Rh-catalyzed asymmetric hydroformylation of **16a** with self-prepared xylose-based phosphite-phosphoramidite ligands **25a,b,d-g** and **26b,d-g**.[a]

Entry	Ligand	Conv. [%]	17a[b] [%]	18a[b] [%]	19a[b] [%]	ee[c] [%]
1	**25a**	97	93	1	2	6 (+)
2	**25b**	>99	97	<1	2	12 (+)
3	**25d**	99	95	<1	3	11 (+)
4	**25e**	96	92	2	2	6 (+)
5	**25f**	>99	97	1	2	12 (+)
6	**25g**	>99	97	<1	2	19 (+)
7	**26b**	100	96	1	3	55 (–)
8	**26d**	98	94	1	4	46 (–)
9	**26e**	100	97	<1	3	48 (–)
10	**26f**	100	96	<1	3	53 (–)
11	**26g**	100	96	<1	3	52 (–)

[a] 0.5 mmol of **16a**, $Rh(acac)(CO)_2$ 5.0 µmol, PP-ligand 6.0 µmol, CO/H_2 = 1:1, 5 mL of toluene, 80 °C, 1.0 MPa, S/Rh = 100, 21 h.
[b] Conversions and yields were determined by ^{31}P NMR spectroscopy.
[c] Ee-values of the linear aldehyde (**17a**) were determined by GC analysis.

Using ligands **25a,b,d-g**, based on (*S*)-BINOL, excellent conversions and regioselectivities to the linear aldehyde were observed, whereas hydrogenation could be suppressed. Unfortunately, the stereodifferentiation was negligible (entries 1-6). The reaction with ligands **26b,d-g**, bearing the (*R*)-BINOL fragment, led to moderate ee-values (up to 55 %). Different alkyl substituents at the nitrogen have only a small influence on the conversion, regio- and enantioselectivity. Optimizations were undertaken while using **26f** as ligand **(**Table 27).

Table 27. Optimization of the Rh-catalyzed asymmetric hydroformylation of **16a** with ligand **26f**.[a]

Entry	*T* [°C]	Conv.[b] [%]	17a[b] [%]	18a[b] [%]	19a[b] [%]	ee[c] [%]
1[d]	80	100	96	<1	3	53 (–)
2[e]	80	25	23	<1	2	57 (–)
3	60	95	89	3	3	61 (–)
4	50	90	84	3	3	62 (–)
5	40	54	48	4	2	63 (–)

[a] 0.5 mmol of **16a**, $Rh(acac)(CO)_2$ 5.0 µmol, **26f** 6.0 µmol, CO/H_2 = 1:1, 5 mL of toluene, *T*, 1.0 MPa, S/Rh = 100, 21 h.
[b] Conversions and yields were determined by ^{31}P NMR spectroscopy.
[c] Ee-values of the linear aldehyde (**17a**) were determined by GC analysis.
[d] Reaction was performed in EtOAc.
[e] Reaction was performed in DCM.

The reaction, performed in EtOAc, gave almost the same results as in toluene from any point of view. When DCM was used as solvent the conversion decreased dramatically to 25 %, although the enantioselectivity slightly increased (entry 2). When the temperature was lowered to 60 °C, the reactivity remained almost unchanged, while the stereoselectivity could be improved to 61 %

(entry 3). Further temperature decrease to 50 °C was accompanied by a slight decline of conversion, but did not influence the ee-value. At 40 °C, the yield of the linear aldehyde seriously dropped to 48 % (entries 4,5).

In the end, mixed phosphite-phosphoramidite ligands **28a-g,i** were also tested in the asymmetric hydroformylation of **16a** (Table 28).

Table 28. Screening of the Rh-catalyzed asymmetric hydroformylation of **16a** with self-prepared xylose-based mixed phosphite-phosphoramidite ligands **28a-g,i**.[a]

Entry	Ligand	Conv.[b] [%]	17a[b] [%]	18a[b] [%]	19a[b] [%]	ee[c] [%]
1	**28a**	49	44	–	5	7 (–)
2	**28b**	47	42	<1	5	5 (–)
3	**28c**	53	50	1	2	10 (–)
4	**28d**	83	75	1	7	1 (+)
5	**28e**	54	50	<1	3	4 (+)
6	**28f**	64	59	<1	5	12 (–)
7	**28g**	>99	89	<1	10	12 (–)
8	**28i**	97	80	–	17	31 (+)

[a] 0.5 mmol of **16a**, $Rh(acac)(CO)_2$ 5.0 µmol, PP-ligand 6.0 µmol, CO/H_2 = 1:1, 5 mL of toluene, 80 °C, 1.0 MPa, S/Rh = 100, 21 h.
[b] Conversions and yields were determined by ^{31}P NMR spectroscopy.
[c] Ee-values of the linear aldehyde (**17a**) were determined by GC analysis.

All ligands with different diol rests at both phosphorus atoms generated significant amounts of the hydrogenation product. Moreover, they showed disappointingly low activities, except for **28g,i**. With these two ligands, almost full conversions resulted. A considerable stereodifferentiation could not be obtained in any case (maximum 31 %ee).

The product, dimethyl (3-oxo-1-phenylpropyl)phosphonate **17a**, has a slightly acidic hydrogen atom at the chiral center. For that reason, it should be taken into consideration that the enantioselectivity might deteriorate during the reaction. To ensure that this undesired side reaction does not happen samples were taken at certain periods and examined with regard to conversion, yields and especially ee-values. A model reaction of the asymmetric hydroformylation of **16a** was performed with $Rh(acac)(CO)_2$ and **26f** in toluene at 80 °C under 1 MPa syngas atmosphere (according to Table 26, entry 10).

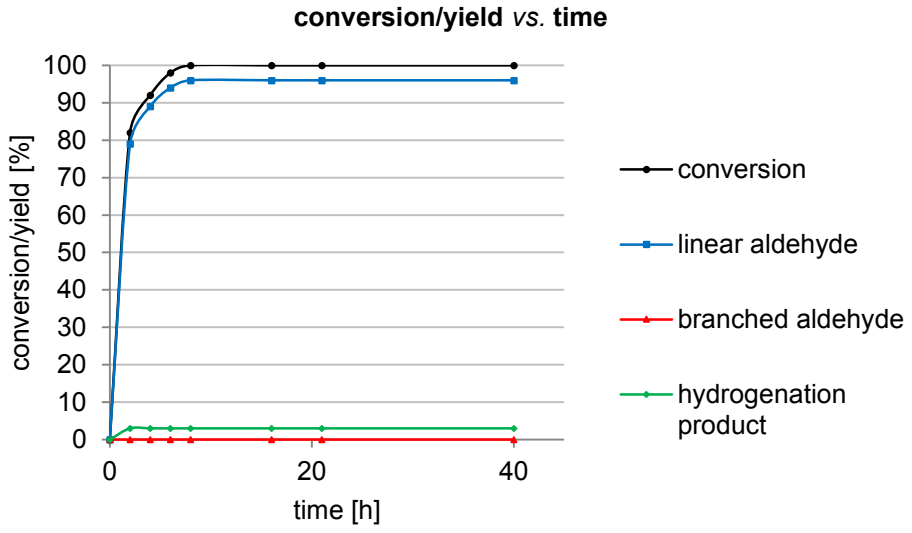


Figure 18. Conversion and yields of the products of the asymmetric hydroformylation of **16a** with $Rh(acac)(CO)_2$ and **26f** over time.

The diagram shows the dependence of the conversion and the yield as a function of reaction time. At a time point of 2 h, 82 % of the starting material were consumed and after approximately 8 h almost full conversion was reached (the black curve). The level of the branched aldehyde was constantly low (<1 %, the red curve) over the whole reaction time. After 2 h, the hydrogenation adjusted to an amount of ca. 3 % of the final product mixture (the green curve). The β-aldehyde is formed at the beginning of the reaction and after 7-8 h, no changes in the formation rate could be detected (the blue curve). Furthermore it can be noted that no decomposition of any product took place after 8 h of reaction (at 80 °C and syngas atmosphere). Additionally, the enantiomeric excess of linear aldehyde **17a** was verified at each time.

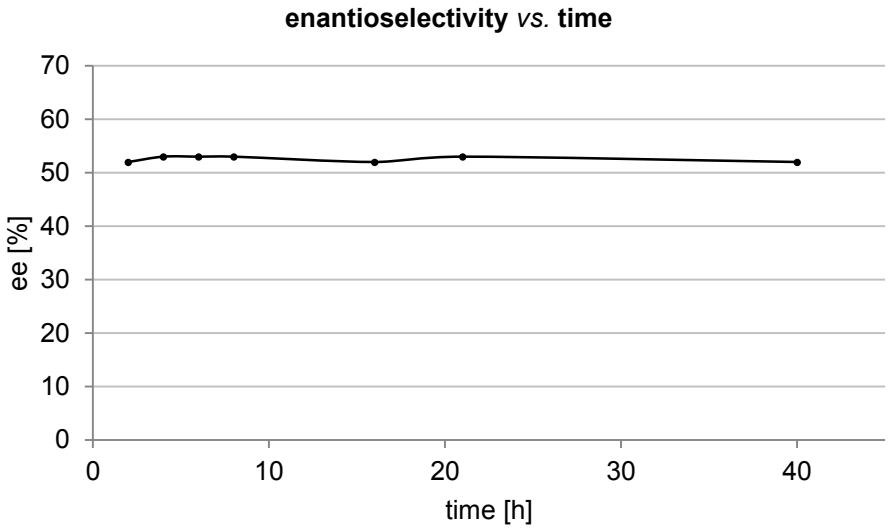
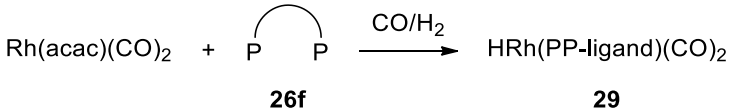


Figure 19. Enantiomeric excess of **17a** as product of the asymmetric hydroformylation of **16a** with $Rh(acac)(CO)_2$ and **26f** over time

It can be concluded that the ee-value remained almost constant after a time of 2 h. When full conversion of the substrate was reached (after ca. 7-8 h), e.g. when the maximum amount of the linear aldehyde was formed, the ee-value did not change (52-53 %) so that racemization of **17a** can be excluded.

3.2.2.5 HP-NMR experiments

Furthermore, it was also possible to record HP-NMR spectra of the catalytic active species[i] for the representative ligand **26f**. Therefore, HRh(**26f**)$(CO)_2$ **29** was prepared *in situ* under hydroformylation conditions to analyze, what configuration the ligand adopts in the complex (Scheme 45).



Scheme 45. Formation of the catalytically active hydridorhodium phosphite-phosphoramidite dicarbonyl-complex HRh(**26f**)$(CO)_2$ **29**.

1.0 Eq of phosphite-phosphoramidite ligand **26f** was added to 1.0 eq of $Rh(acac)(CO)_2$ in C_6D_6. This solution was purged with 1.0 MPa syngas and shaken at 80 °C for 21 h. Subsequently, the solution

[i] HP-NMR experiments were performed in cooperation with Dr. Baumann at Leibniz-Institut für Katalyse e.V. in Rostock/Germany and Prof. Diéguez at Universitat Rovira í Virgili in Tarragona/Spain.

was measured under atmospheric pressure and indicated the formation of HRh(**26f**)$(CO)_2$-complex **29** (Table 29). The ^{1}H NMR spectrum, shown in Figure 21, illustrates the characteristic region for the hydride.

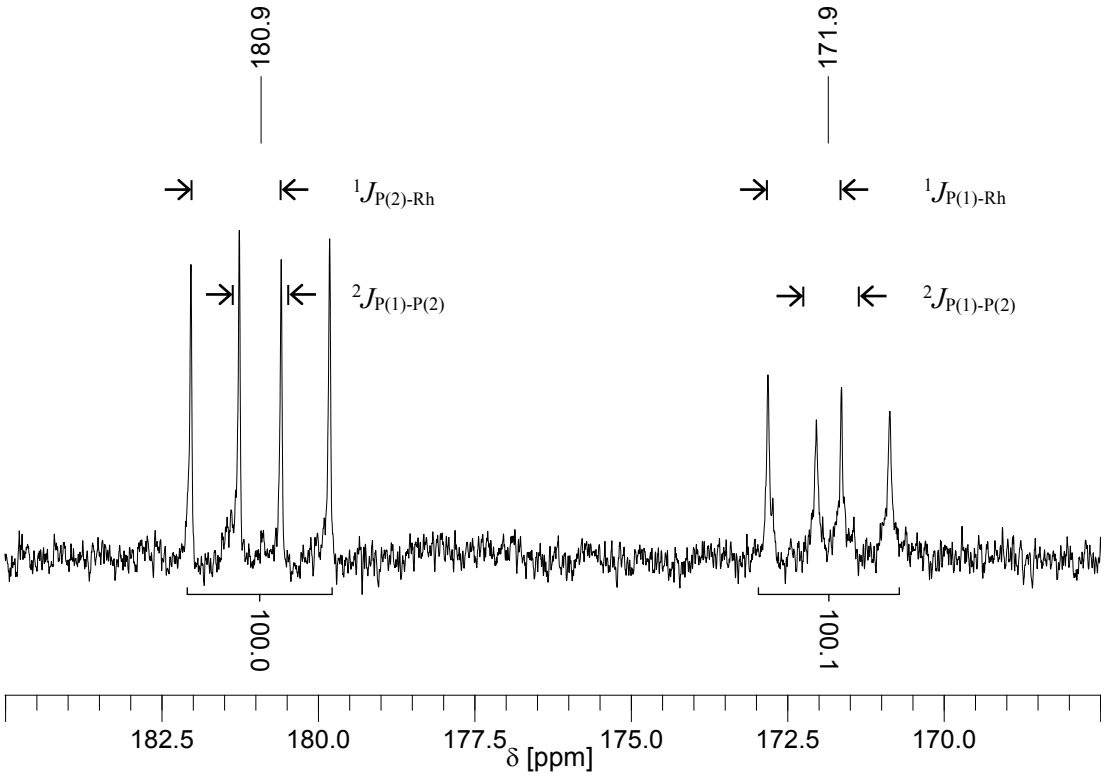


Figure 20. ^{31}P NMR for the hydridorhodium phosphite-phosphoramidite dicarbonyl-complex HRh(**26f**)$(CO)_2$ **29**.

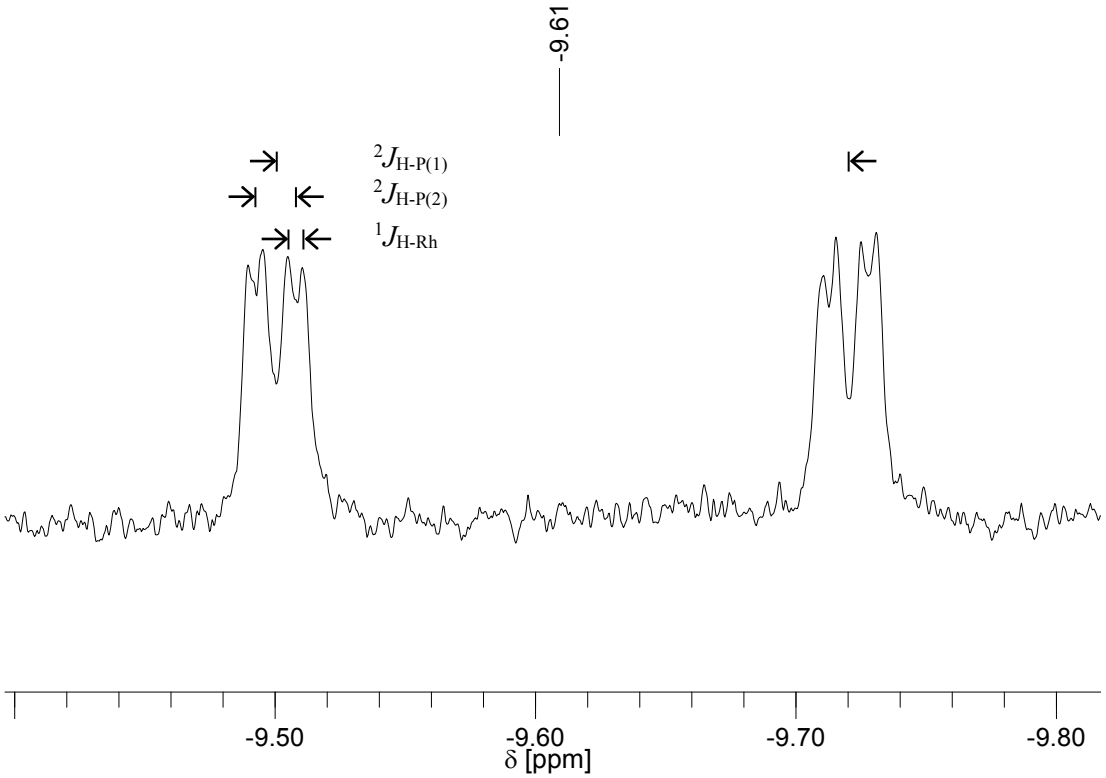


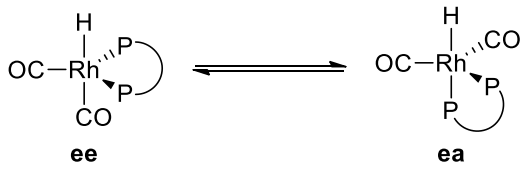
Figure 21. ^{1}H NMR for the hydridorhodium phosphite-phosphoramidite dicarbonyl-complex HRh(**26f**)$(CO)_2$ **29**.

Table 29. ^{1}H and ^{31}P NMR data for HRh(**26f**)(CO)$_2$-complex **29**.[a]

δ(P(1))	δ(P(2))	$^{1}J_{P(1)-Rh}$	$^{1}J_{P(2)-Rh}$	$^{2}J_{P(1)-P(2)}$	δ(H)	$^{2}J_{H-P(1)}$	$^{2}J_{H-P(2)}$	$^{1}J_{H-Rh}$
171.9 (dd)	180.9 (dd)	190.1	233.3	124.7	-9.61 (ddd)	88.0	6.0	2.0

[a] Prepared in toluene-d_8; NMR spectra were recorded under atmospheric conditions at room temperature; chemical shift δ in ppm; coupling constant J in Hz.

In ^{31}P NMR spectrum a set of two double doublets can be seen. They result from two non-equivalent phosphorus atoms, which couple to each other and also to rhodium. The signals appear at δ(P(1)) = 171.9 ppm and at δ(P(2)) = 180.9 ppm. The coupling constants for ^{31}P(1)-^{103}Rh is $^{1}J_{P(1)-Rh}$ = 190.1 Hz, what neither corresponds to a complete equatorial nor to a complete apical coordination.[21a] The coupling constant between ^{31}P(2)-^{103}Rh equals $^{1}J_{P(2)-Rh}$ = 233.2 Hz and is typical for an equatorial coordination of the phosphorus to rhodium.[21a]
The ^{31}P(1)-^{31}P(2) coupling constant is $^{2}J_{P(1)-P(2)}$ = 124.7 Hz. This is lower than for an ideal bisequatorial coordination of both phosphorus atoms, what ranges between 235-240 Hz,[21a] but higher than for equatorial-axial complexes (0-70 Hz). The observation might suggest that there is a dynamic equilibrium between **ee**- and **ea**-coordination that leads to an averaged value for the chemical shifts (δ) and the coupling constant ($^{2}J_{P(1)-P(2)}$, Scheme 46). Another aspect, what has to be considered, is the possible formation of a distorted trigonal bipyramidal hydridorhodium dicarbonyl species with **ee**-coordination.[120]

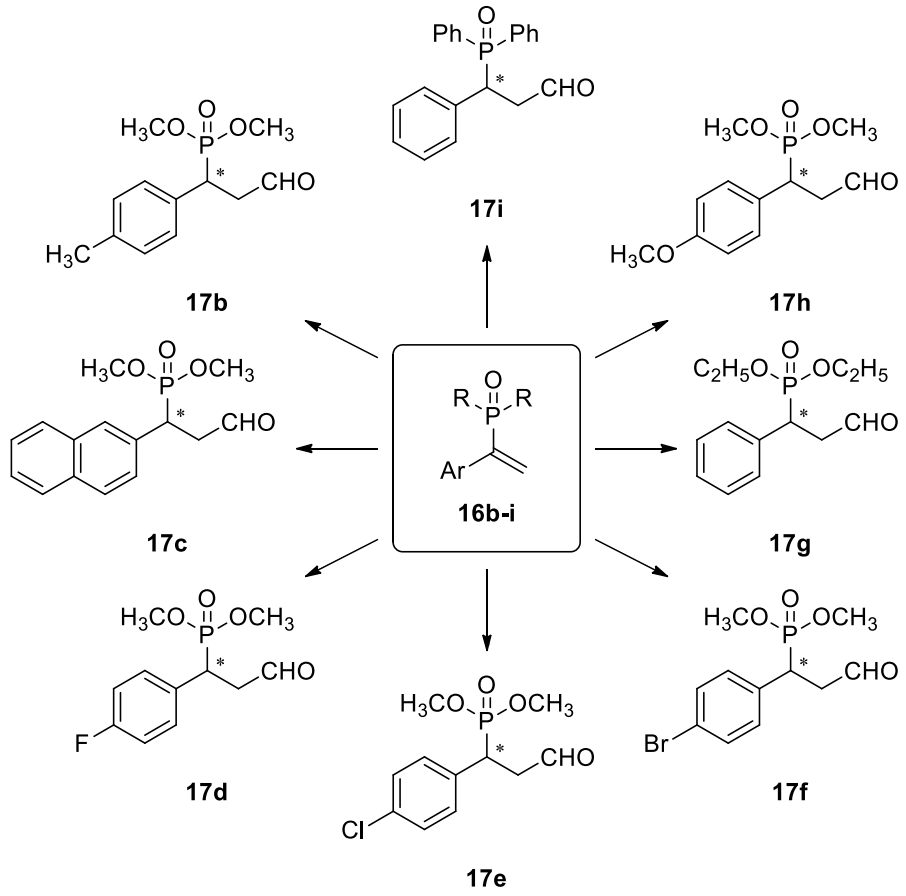


Scheme 46. Equilibrium of two rhodium-complexes with equatorial-equatorial (**ee**) and equatorial-apical (**ea**) coordination of the bidentate ligand.

The reason, why there is only one double doublet for each phosphorus instead of the estimated double set of double doublets, is the fast exchange of the position of the phosphorus, which cannot be determined on the NMR time scale.[25c]
In the ^{1}H NMR spectrum, a doublet of double doublets at δ(H) = -9.60 ppm is visible that can be assigned to the apical position of the hydride. The coupling constant for ^{1}H-^{31}P, $^{2}J_{H-P(1)}$ = 88.0 Hz, is an averaged value[25c] between the characteristical one for an equatorial (J < 10 Hz) and an axial coordination (J = 140-200 Hz[21a]). Therefore, it can be assigned to the coupling between the hydride and the phosphorus P(1). The other coupling constant mounts to $^{2}J_{H-P(2)}$ = 6.0 Hz. It is typical for an equatorial coordination and belongs to the coupling between the hydride and the phosphorus P(2). The value of ^{1}H-^{103}Rh is $^{1}J_{H-Rh}$ = 2.0 Hz is usual.[120a]
In conclusion, it can be summarized that the values for $^{2}J_{H-P}$ and $^{2}J_{P(1)-P(2)}$ indicate a fast exchange between **ee**- and **ea**-coordination, but no dominant geometry can be supposed. One phosphorus atom changes its position and is located at the equatorial as well as the apical position in the trigonal bipyramidal-complex.

3.2.2.6 Scope of the asymmetric hydroformylation of α-phosphorylated vinyl arenes

We tried to expand the scope to a variety of substrates **16b-i** for the asymmetric hydroformylation (Scheme 47). The reaction was performed with the L-(–)-ephedrine-based ligand **22b** and the α-D-xylose- and amino xylose-based ligands **L6e** and **26f**, respectively. A temperature of 80 °C and a syngas pressure of 1 MPa were chosen as reaction conditions.



Scheme 47. Scope of the asymmetric hydroformylation of **16b-i**.

Table 30. Scope of the Rh-catalyzed asymmetric hydroformylation of **16b-i** with ligands **22b**, **L6e** and **26f**.[a]

Entry	Substrate	Ligand	Conv.[b] [%]	17[b] [%]	18[b] [%]	19[b] [%]	ee[c] [%]
1	**16b**	**22b**	72	67	<1	4	n.d.[d]
2	**16b**	**L6e**	90	80	–	10	n.d.[d]
3	**16b**	**26f**	100	95	1	4	n.d.[d]
4	**16h**	**22b**	77	75	<1	1	n.d.[d]
5	**16h**	**L6e**	79	75	<1	3	n.d.[d]
6	**16h**	**26f**	100	99	<1	1	n.d.[d]
7	**16c**	**22b**	72	60	2	10	n.d.[d]
8	**16c**	**L6e**	97	81	–	16	n.d.[d]
9	**16c**	**26f**	>99	94	1	4	n.d.[d]
10	**16d**	**22b**	67	62	<1	4	17 (+)
11	**16d**	**L6e**	94	89	<1	5	3 (+)
12	**16d**	**26f**	100	96	<1	3	36 (–)
13	**16e**	**22b**	65	58	1	6	17 (+)
14	**16e**	**L6e**	98	88	1	10	1 (+)
15	**16e**	**26f**	100	95	1	4	35 (–)
16	**16f**	**22b**	66	57	1	9	19 (+)
17	**16f**	**L6e**	97	89	<1	7	2 (+)
18	**16f**	**26f**	100	95	1	4	37 (–)
19	**16g**	**22b**	99	97	<1	2	n.d.[d]
20	**16g**	**L6e**	90	86	<1	3	n.d.[d]
21	**16g**	**26f**	>99	95	<1	5	n.d.[d]
22	**16i**	**22b**	83	74	–	9	n.d.[d]
23	**16i**	**L6e**	97	67	–	30	n.d.[d]
24	**16i**	**26f**	100	89	–	11	n.d.[d]

[a] 0.5 mmol of substrate, $Rh(acac)(CO)_2$ 5.0 µmol, PP-ligand 6.0 µmol, CO/H_2 = 1:1, 5 mL of toluene, 80 °C, 1.0 MPa, S/Rh = 100, 21 h.
[b] Conversions and yields were determined by ^{31}P NMR spectroscopy.
[c] Ee-values of the linear aldehyde (**17**) were determined by GC analysis.
[d] Up to now, the degree of enantioselectivity could not be determined, even not by application of different GC and HPLC columns.

As a general tendency, best conversions of the substrates and yields to the corresponding aldehydes were observed with **26f**.

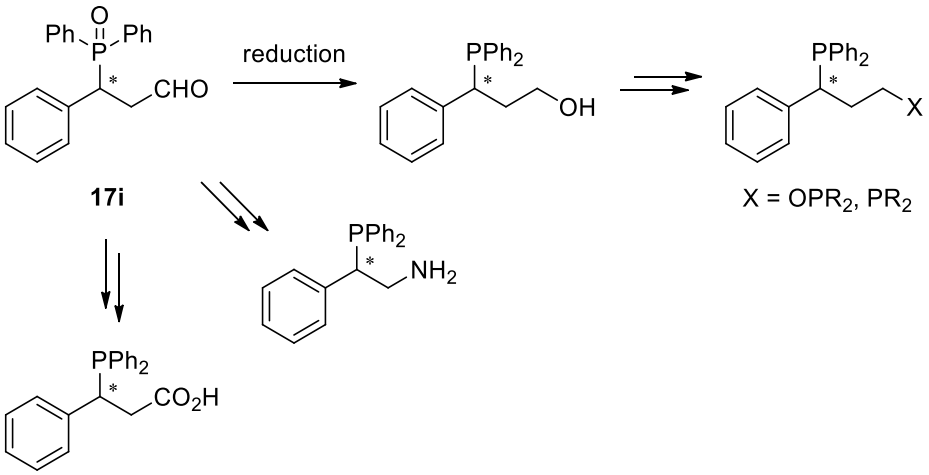
The hydroformylation of substrates **16b** and **16h**, which have electron donating groups (methyl group for **16b**, [+*I*-effect] or methoxy group for **16h** [+*M*-effect]) in the *para*-position of the aryl ring, resulted in full conversions with ligand **26f** (entries 3,6). Stereoselectivities were not indicated, because the enantiomers could not be separated.

For substrates **16d-f**, possessing electron withdrawing groups in the *para*-position of the aryl ring (different halogens, –*I*-effect), hydroformylation with ligand **22b** gave moderate conversions (ca. 70 %), but low ee-values (entries 10,13,16). Moreover, trials with **L6e** as ligand resulted in almost full conversion, but hydrogenation occurred up to 10 % and the stereodifferentiation was surprisingly poor. When ligand **26f** was used, very good rates to the linear aldehyde were achieved, however, the maximum of the reached enantiomeric excess was only 37 %.

When diethyl phosphonate **16g** was submitted to the reaction, results with these three ligands were comparable to those of the dimethyl phosphonate **16a**. The ethyl group does not seem to have a great influence on conversion, regio-, chemoselectivity. A yield of 95 % for the linear aldehyde was reached with ligand **26f**. A stereoselectivity was not determined, because both enantiomers could not be separated (entries 19-21). In the reaction of phosphine oxide **16i**, having a different steric environment at the phosphorus atom (phenyl instead of alkoxy groups), the hydrogenation was promoted (up to 30 %, (entries 22-24). Obviously, the steric demanding phenyl groups shield the double bond so that only small molecules (like H_2) can attack, what leads to enhanced hydrogenation.

3.2.2.7 Outlook

The synthesis of enantiopure 3-aryl-3-phosphorylated propanals will remain an interesting task since a range of interesting structures can be derived. For example, both, phosphine oxide and aldehyde group in **17i**, could be reduced to give the corresponding hydroxy phosphine compound, which may serve itself as ligand or on the way to more sophisticated ligands (Scheme 48).



Scheme 48. Subsequent transformations starting from phosphine oxide **17i**.

Moreover, the aldehyde can also be converted into a variety of functionalized compounds, e.g. alcohols, amines and carbon acids and their derivatives.

3.2.3 Preparation of enantioenriched 3-phenyl butanal

3-Phenyl butanal has a grassy, fresh and floral odor.[i] Together with several derivatives, such as Florhydral®,[ii] it is used as fragrance in all areas of perfumery, due to its great intensity.

The scaffold of enantiomerically pure 3-phenyl butanal becomes apparent as substructure of 3-aryl γ-aminobutyric acid and can be found, for example, in Phenibut (Figure 22). Its (*R*)-enantiomer is pharmacologically active and shows anxiolytic effects in humans and animals. It is used for post-traumatic stress disorder, anxiety and insomnia, but also for treatment of alcoholism (withdrawal).[121]

The structurally related derivative (*R*)-Baclofen is a specific agonist at the $GABA_B$-receptor of mammals. It is applied for treatment of spasticity and acts as a muscle relaxant.[122]

(*R*)-Rolipram (Figure 22) has an antidepressive,[123] antipsychotic,[124] anti-inflammatory, immunosuppressive,[125] and anti-tumor effect.[126]

[i] 3-Phenyl butanal is also known as hyacinth butanal or Triferal®.

[ii] The chemical name for Florhydral® (floral butanal) is 3-(3-isopropylphenyl)butanal. Currently, Florhydral® is predominantly supplied by Givaudan SA.

(*R*)-Phenibut R = H
(*R*)-Baclofen R = Cl

(*R*)-Rolipram

Figure 22. Chiral pharmaceuticals derived from 3-phenyl butanal: (*R*)-Phenibut, (*R*)-Baclofen and (*R*)-Rolipram.

Up to now, a variety of different synthetic strategies for the synthesis of chiral 3-phenyl butanal have been tested with more or less success with respect to yield and selectivity. Early research was focused on the diastereoselective addition of different organometallic compounds to allylamines,[127] allyl ethers,[128] α,β-unsaturated aldimines,[129] acetals[130] or oxazolidines[131] using diverse chiral auxiliars. Moreover, copper-catalyzed 1,4-addition[132] became attractive, too.

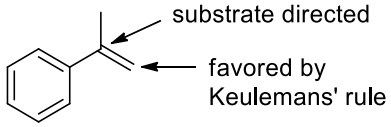
Another method for the preparation is based on the enantioselective isomerization of β-methyl cinnamyl alcohol. With a homogeneous rhodium-complex as catalyst,[133] excellent yields and up to 75%ee could be reached. However, high amounts of catalyst were needed. The ruthenium-[134] and iridium-catalyzed[135] reactions generated high ee's, but only moderate yields.

The asymmetric transfer hydrogenation of β-methyl cinnamaldehyde, using the Hantzsch ester,[136] illustrated another route to yield 3-phenyl butanal with enantioselectivities up to 94 %.[137] In this context, other hydrogen sources were employed, too, but competitive hydrogenation to the unsaturated alcohol could not be suppressed.[138]

Asymmetric hydroformylation of α-methyl styrene, a cheap and available compound from large industrial-scale,[i] represents a suitable alternative to get chiral 3-phenyl butanal as well as its derivatives.

3.2.3.1 Asymmetric hydroformylation of α-methyl styrene

The reaction under hydroformylation conditions can give chiral aldehyde **30**, branched (achiral) aldehyde **31** and hydrogenation product cumene (Scheme 49). In principle, an interesting competition in the reaction pathways between the preferred terminal aldehyde, according to Keulemans' rule, and the *iso*-product due to the α-regiodirecting effect of the styrene can be expected (Figure 23).

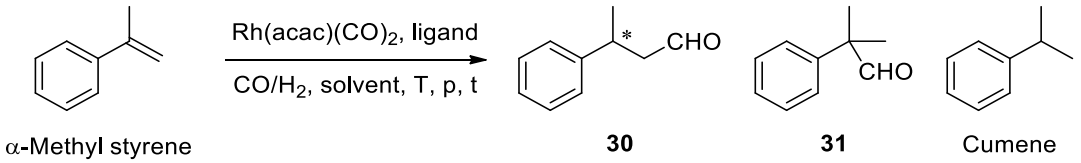


α-Methyl styrene

Figure 23. Regioselective binding of the CHO-group.

Since we aimed to get the chiral product, we started promptly with chiral rhodium catalysts (Table 31).

[i] α-Methyl styrene is a side product in the cumene process.[139]



Scheme 49. Asymmetric hydroformylation of α-methyl styrene.

Table 31. Initial trials of the Rh-catalyzed asymmetric hydroformylation of α-methyl styrene with commercial ligands.[a]

Entry	Ligand	Conv.[b] [%]	30[b] [%]	31[b] [%]	Cumene[b] [%]	ee[c] [%]
1	(*S*,*S*)-DIOP	94	90	1	3	rac
2	(*S*,*S*)-BDPP	83	80	1	3	rac
3	(*R*)-SynPhos	71	69	1	1	1 (–)
4	(*R*,*R*)-Me-DuPhos	35	31	1	3	rac
5	(*S*,*S*)-ChiraPhos	76	66	<1	10	1 (+)
6	(*R*,*R*)-DIPAMP	18	14	1	3	rac
7	(*R*)-DifluorPhos	69	64	2	3	rac
8	(*R*,*R*)-Ph-BPE	70	65	2	3	9 (+)
9	(*R*,*R*)-QuinoxP*	43	18	14	11	15 (–)
10	(*S*,*S*)-BenzP*	100	86	–	14	rac
11	(*R*,*R*)-Chiraphite	87	85	1	2	1 (+)
12	(*R*,*R*)-Kelliphite	95	92	<1	3	1 (–)

[a] 0.5 mmol of α-methyl styrene, $Rh(acac)(CO)_2$ 5.0 µmol, PP-ligand 6.0 µmol, CO/H_2 = 1:1, 5 mL of toluene, 80 °C, 1.0 MPa, S/Rh = 100, 21 h.
[b] Conversions and yields were determined by ^1H NMR spectroscopy.
[c] Ee-values of the linear aldehyde (**30**) were determined by GC analysis.

According to the hydroformylation of **16a** we adopted the conditions (amount of catalyst, temperature, pressure, time) and started with $Rh(acac)(CO)_2$ and commercially available chiral ligands. At 80 °C and under 1 MPa syngas atmosphere, conversions from 18 % to 94 % were obtained (entries 1-7). The formation of the linear aldehyde was privileged, however, small amounts of the branched aldehyde and the hydrogenation product were found in all cases. With rhodium catalysis, based on these ligands, it was not able to induce any chirality in the final product; almost racemic mixtures of 3-phenyl butanal were determined.

When recently successful ligands in the asymmetric hydroformylation (see Chapter 2.2.2.2) were applied, no improvements could be achieved: with (*R*,*R*)-Ph-BPE a moderate conversion (70 %) with poor enantioselectivity (9 %ee) was obtained (entry 8). (*R*,*R*)-QuinoxP* and (*S*,*S*)-BenzP* gave the linear aldehyde in only 15 %ee and as a racemic mixture, respectively (entries 9,10).

The reaction with diphosphites, such as (*R*,*R*)-Chiraphite and (*R*,*R*)-Kelliphite, resulted in good conversions and excellent regioselectivities. Nevertheless, both ligands were not able to induce considerable enantioselectivities as well (entries 11,12). The unsatisfying results prompted us to switch to our self-prepared ligands (Table 32).

Table 32. Screening of the Rh-catalyzed asymmetric hydroformylation of α-methyl styrene with self-prepared diphosphite ligands **21a-e** and phosphite-phosphoramidite ligand **22b**.[a]

Entry	Ligand	Conv.[b] [%]	30[b] [%]	31[b] [%]	Cumene[b] [%]	ee[c] [%]
1	**21a**	97	97	<1	–	2 (+)
2	**21b**	97	96	1	–	33 (–)
3	**21c**	76	75	1	–	8 (–)
4	**21d**	74	73	1	–	4 (–)
5	**21e**	91	90	<1	1	18 (–)
6	**22b**	87	85	2	–	10 (–)

[a] 0.5 mmol of α-methyl styrene, $Rh(acac)(CO)_2$ 5.0 µmol, PP-ligand 6.0 µmol, CO/H_2 = 1:1, 5 mL of toluene, 80 °C, 1.0 MPa, S/Rh = 100, 21 h.
[b] Conversions and yields were determined by ^1H NMR spectroscopy.
[c] Ee-values of the linear aldehyde (**30**) were determined by GC analysis.

We started our trials with chiral diphosphites **21a-e** and obtained conversions up to 97 %. However, the rhodium catalysts, based on these structurally related ligands, varied in reactivity and stereodifferentiation. Excellent chemo- and regioselectivities were attained in all cases (entries 1-5). When **21b** was employed, a good enantioselectivity for the linear aldehyde was observed (33 %ee). L-(–)-Ephedrine-based phosphite-phosphoramidite **22b** gave a satisfying conversion accompanied by a poor ee-value of 10 % (entry 6).
Finally, we performed the asymmetric hydroformylation of α-methyl styrene using the xylose-based ligands (Table 33).

Table 33. Screening of the Rh-catalyzed asymmetric hydroformylation of α-methyl styrene with self-prepared xylose-based phosphite-phosphoramidite ligands **25a,d-g**, **26d-g** and **28a-g,i**.[a]

Entry	Ligand	Conv.[b] [%]	30[b] [%]	31[b] [%]	Cumene[b] [%]	ee[c] [%]
1	**25a**	83	81	1	1	23 (+)
2	**25d**	92	88	1	3	10 (+)
3	**25e**	88	86	1	1	12 (+)
4	**25f**	82	80	1	1	36 (+)
5	**25g**	96	95	<1	–	39 (+)
6	**26d**	86	83	2	1	14 (–)
7	**26e**	93	91	1	1	8 (–)
8	**26f**	91	89	2	–	14 (–)
9	**26g**	91	87	2	2	20 (–)
10	**28a**	67	63	1	3	11 (–)
11	**28b**	65	63	1	<1	9 (–)
12	**28c**	74	72	2	–	15 (–)
13	**28d**	96	93	1	2	rac
14	**28e**	46	45	1	–	2 (–)
15	**28f**	58	57	<1	–	5 (–)
16	**28g**	98	92	1	5	16 (–)
17	**28i**	91	87	1	3	18 (+)

[a] 0.5 mmol of α-methyl styrene, $Rh(acac)(CO)_2$ 5.0 µmol, PP-ligand 6.0 µmol, CO/H_2 = 1:1, 5 mL of toluene, 80 °C, 1.0 MPa, S/Rh = 100, 21 h.
[b] Conversions and yields were determined by ^1H NMR spectroscopy.
[c] Ee-values of the linear aldehyde (**30**) were determined by GC analysis.

First of all, it could be noted that the substituents at the *N*-moiety of ligands **25** and **26** have a crucial effect on the hydroformylation of α-methyl styrene and this fact is in contrast to the reaction of **16a**. When a rhodium catalyst was used, what is based on **26a** (containing *N*-Me), 23 %ee for the linear aldehyde were reached (entry 1). Ligands with more sterically demanding substituents at the nitrogen atom, such as cyclohexyl and phenyl (represented in **25d** and **25e**, respectively), gave lower enantioselectivities (entries 2,3). Surprisingly, ligand **25f**, bearing a benzyl group at the nitrogen,

managed to induce a stereoselectivity of 36 % (entry 4) that could be slightly exceeded by application of **25g** (39 %ee, entry 5).
For all these ligands, conversions up to 96 % and very good yields (up to 95 %) to the desired 3-phenyl butanal were attained.
Hydroformylation with ligands, bearing (*R*)-BINOLs at both phosphorus atoms (**26d-g**), showed similar results with respect to reactivity and regioselectivity. However, lower enantioselectivities were detected in all cases (entries 6-9).
When mixed xylose-based phosphite-phosphoramidites were used, varying conversions were obtained depending on the substituents at the phosphorus atoms. Among these trials, only ligands **28d** and **28g** induced high yields of linear aldehyde (93 % and 92 %, respectively, entries 13,16). Unfortunately, no general tendency can be recognized, how the substituents at the phosphorus atoms are related to reactivity as well as to the stereocontrol of the chiral catalyst.
Summarizing, it can be said that α-methyl styrene was hydroformylated yielding 95 % of the desired linear aldehyde. This product could be obtained in 39 %ee using the self-prepared ligand **25g**.

4 Summary and outlook

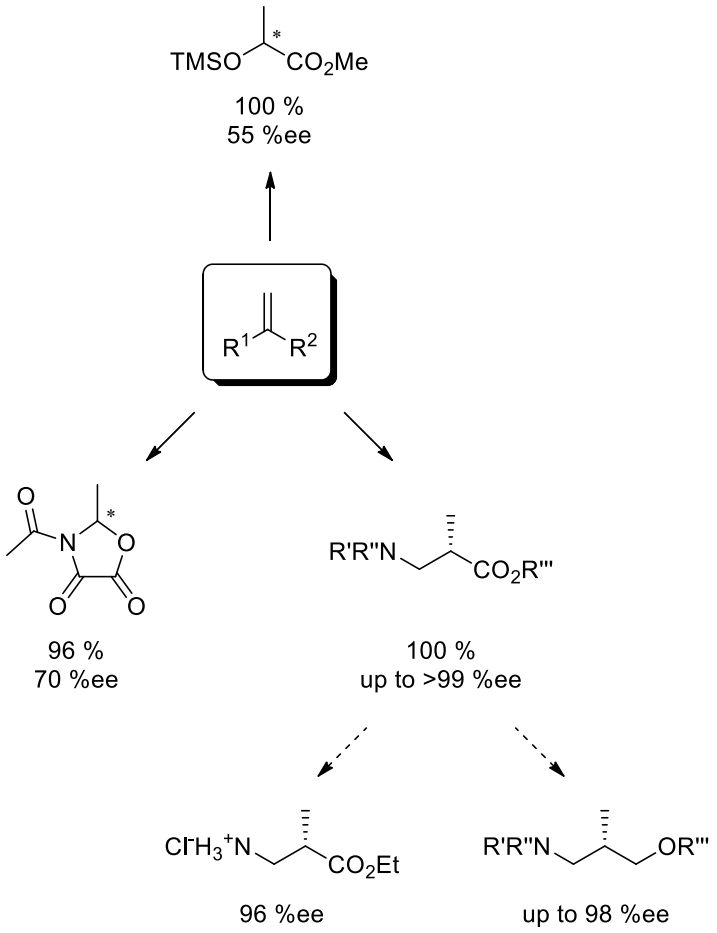
The general aim of this thesis consisted in the examination of the asymmetric hydrogenation and the hydroformylation of 1,1-disubstituted olefins as an alternative approach to the synthesis of new or known chemical compounds or substructures.

First part of this dissertation was devoted to the asymmetric hydrogenation of functionalized olefins. With the hydrogenation of trimethylsilylated dehydro lactate, a new strategy to the synthesis of an *O*-protected lactic acid derivative could be established. In this context, different catalyst precursors were tested and the performance of the superior system was optimized with respect to yield and stereodifferentiation. Catalysts, recently applied for structurally related substrates, did not perform successfully. Noteworthy, a corresponding three-fold substituted olefin did not react under the optimized conditions. Even a more severe reaction regime afforded only inferior results. A broader catalyst screening, preferentially based on high-throughput screening, could probably give more promising results. Unfortunately, such devices were not accessible during this thesis.

In addition, the stereoselective hydrogenation of a cyclic *N*,*O*-ketene acetal was examined, what represented a great challenge, since this class of olefins was not hydrogenated asymmetrically, yet.

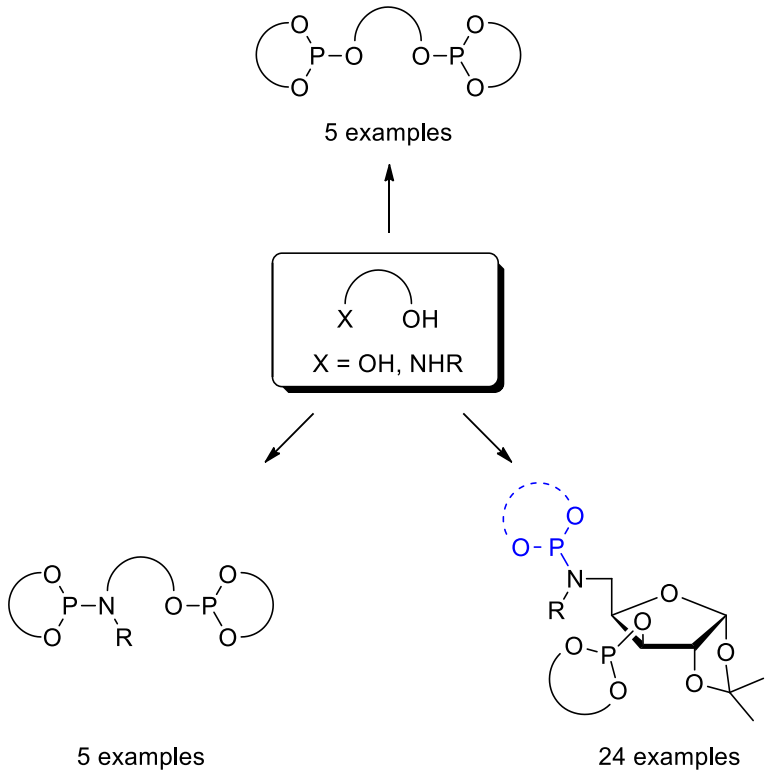
Among numerous catalyst precursors tested, a (*R*,*S*)-JosiPhos-based rhodium system gave superior results after optimization of the reaction parameters. By evaluation of further ligands within this ferrocene-based ligand family, no improvements could be achieved. Resulting cyclic *N*,*O*-acetal was isolated in an excellent yield with good enantioselectivity.

A further aspect of this thesis was the asymmetric hydrogenation of dehydro β^2-homoalanine derivatives. One compound of this class served as a model substrate and was treated with rhodium catalysts using a variety of ligands. With the help of a commercially available ligand, developed in the research group of Prof. Börner, an excellent enantioselectivity and yield could be reached. Further trials with other substrates of this class could be worked out. They showed convincing results as well and proved the wide range of application of this method. In addition, two newly generated β^2-homoalanine derivatives served as starting material for further transformations. Selectively, the ester- as well as the *N*-protecting group could be reduced and further converted, respectively, under preservation of the chiral center to finally yield chiral 1,3-amino alcohols (Scheme 50).



Scheme 50. Asymmetric hydrogenation of 1,1-disubstituted olefins and subsequent transformations.

A further part of this thesis consisted of the synthesis of novel, chiral phosphorus ligands and their application in the asymmetric hydroformylation of 1,1-disubstituted olefins. Next to the preparation of non-commercial ligands, such as (*R*,*S*)- and (*R*,*R*)-BINAPHOS, chiral diphosphites, based on various aromatic diols, were synthesized. The preparation of phosphite-phosphoramidites, derived from 1,2-amino alcohols, was successful and provided five new ligands, which were tested in asymmetric hydroformylation. Furthermore, in cooperation with the research group of Prof. Diéguez (Universitat Rovira í Virgili in Tarragona/Spain), six xylose-based amines were prepared in a four-step synthesis, which were then used as starting material for the synthesis of bidentate phosphite-phosphoramidite ligands on the other hand (12 new compounds). A two-step reaction enabled at first the preparation of monophosphites (three new compounds), which were then converted into mixed phosphite-phosphoramidites. In this manner, nine new ligands were synthesized and tested in asymmetric hydroformylation (Scheme 51).



Scheme 51. Synthesis of new diphosphites and phosphite-phosphoramidites.

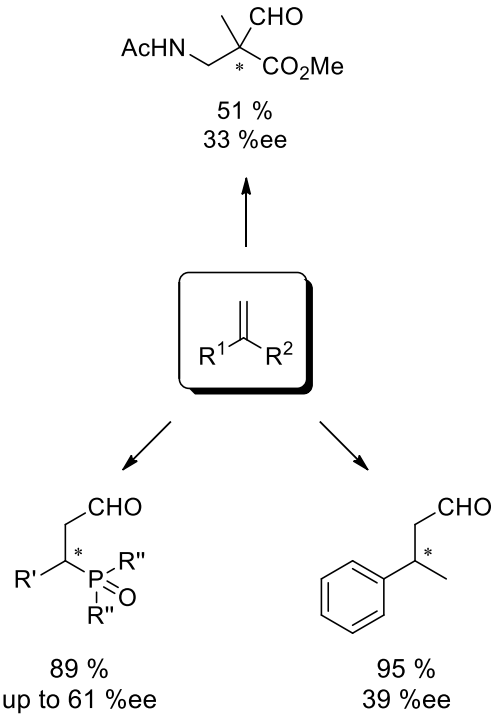
By means of a precatalysts based on a self-prepared xylose-based phosphite-phosphoramidite ligand, HP-NMR experiments were undertaken. The resulting data provided information about the formed hydridorhodium-complex and led to some assumptions of the preferred coordination geometry of the bidentate ligand to the metal.

The asymmetric hydroformylation of a dehydro β^2-homoalanine derivative led mainly to isomerization. The desired branched aldehyde could be obtained in maximum 33 %ee.

Furthermore, an α-phosphorylated styrene derivative was hydroformylated to yield predominately the linear aldehyde. By screening of a set of sugar-based ligands, the desired product resulted convincingly. Optimization, with respect to the conditions and also the application of new self-prepared ligands, led to an excellent yield and promising stereoselectivity. The scope could be extended to eight different substituted α-phosphorylated vinyl arenes and one phosphine oxide derivative.

The asymmetric hydroformylation of α-methyl styrene delivered the linear aldehyde in a very good yield and a moderate enantioselectivity while the reaction was performed with a self-prepared xylose-based phosphite-phosphoramidite ligand (Scheme 52).

In this context, all substrates, with the exception of α-methyl styrene, were self-prepared.



Scheme 52. Asymmetric hydroformylation of 1,1-disubstituted olefins.

In this thesis performed hydrogenation and hydroformylation reactions display a practical alternative to already existing synthesis strategies. Because of the relatively simple transition between both types of reaction, a wide range of various compounds can be easily achieved. Regarding to 1,1-disubstituted olefins, it becomes clear that these compounds possess a great potential, especially in the field of enantioselective hydroformylation. However, up to now, it is a great challenge to handle reactivity as well as chemo-, regio- and stereoselectivity that requires additional investigations in future.

5 Appendix

5.1 Experimental section

5.1.1 Materials and methods

5.1.1.1 General remarks

All non-aqueous reactions were carried out in oven-dried glassware under an argon atmosphere in order to exclude oxygen and/or water (Schlenk techniques were applied). Solvents for the reactions were dried and distilled by standard methods or purchased in extra dry quality from SIGMA ALDRICH®. All chemicals, which were employed, were purchased from a commercial source (SIGMA ALDRICH®, ALFA AESAR®, ABCR) and used as received.

5.1.1.2 Methods for the compound characterization and analysis

^{1}H NMR spectroscopy:

Bruker AVANCE 300 III (f = 300 MHz) and Bruker AVANCE 250 II (f = 250 MHz). All chemical shifts δ are given in ppm. All coupling constants are indicated as *J* and given in Hz. References: tetramethylsilane TMS (δ = 0.00 ppm) was taken as internal standard. Chemical shifts for deuterated solvents: δ = 7.26 ppm for $CDCl_3$, δ = 7.16 ppm for C_6D_6, δ = 5.32 ppm for CD_2Cl_2 and δ = 3.31 ppm for CD_3OD. Peak characterization: s = singlet, d = doublet, dd = double doublet, ddd = doublet of double doublet, t = triplet, q = quartet, dq = double quartet, m = multiplet, br = broad. Aromatic hydrogen atoms are abbreviated as CH-Ar.

^{13}C NMR spectroscopy:

Bruker AVANCE 300 III (f = 75 MHz) and Bruker AVANCE 250 II (f = 63 MHz). All chemical shifts δ are given in ppm. All coupling constants are indicated as *J* and given in Hz. References: tetramethylsilane TMS (δ = 0.00 ppm) was taken as internal standard. Chemical shifts for deuterated solvents: δ = 77.00 ppm for $CDCl_3$ and δ = 128.06 ppm for C_6D_6, δ = 54.00 ppm for CD_2Cl_2 and δ = 49.15 ppm for CD_3OD. Peak characterization: s = singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, m = multiplet, br = broad. DEPT method was used for determining the presence of primary, secondary, tertiary and quaternary carbon atoms. Aromatic carbon atoms are abbreviated as CH_{Ar} and C_{Ar}.

^{19}F NMR spectroscopy:

Bruker AVANCE 300 III (f = 282 MHz). All chemical shifts δ are given in ppm. All coupling constants are indicated as *J* and given in Hz. References: trichlorofluoromethane $CFCl_3$ (δ = 0.00 ppm) was taken as internal standard. Peak characterization: s = singlet, d = doublet.

^{31}P NMR spectroscopy:

Bruker AVANCE 300 III (f = 121 MHz) and Bruker AVANCE 250 II (f = 101 MHz). All chemical shifts δ are given in ppm. All coupling constants are indicated as *J* and given in Hz. References: phosphoric acid H_3PO_4 (δ = 0.00 ppm) was taken as internal standard. Peak characterization: s = singlet, d = doublet, dd = double doublet, br = broad.

Mass spectrometry (MS):

Finnigan MAT 95-XP (ThermoElectron, EI, 70 eV) and Agilent-6890 with Agilent-5973 mass spectrometer.

High resolution mass spectrometry (HRMS):

Agilent 6210 E1969A TOF. Only the measurements with an average deviation from the theoretical mass of ± 2 mDa were accounted as correct.

Gas chromatography (GC):

Agilent-7890A with flame ionization detector (FID).

High pressure liquid chromatography (HPLC):

HP 1100 (Hewlett Packard) with diode array detector (DAD).

Elemental analysis (EA):

C/H/N/S-Microanalysator TruSpec CHNS (Leco).

Polarimetry:

Gyromat-HP High Precision Digital Automatic Polarimeter (Kernchen, Germany). The length of the cuvettes were l_1 = 10 mm and l_2 = 20 mm; the wavelength is λ = 589 nm.

Melting point determination (mp):

Micro-Hot-Stage Galen™ III Cambridge Instruments. The melting points were not corrected.

5.1.2 Synthesis methods

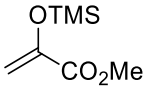
5.1.2.1 Synthesis of 2-[(trimethylsilyl)oxy] esters

General procedure for the synthesis of α,β-unsaturated methyl esters **1a,b**

The α-keto ester (1.0 eq) is dissolved in dichloromethane (1 mL/1.0 mmol substrate) and chlorotrimethylsilane (1.4 eq) is added. Then, triethylamine (1.6 eq) is added dropwise to the solution, which is stirred at room temperature for 16 h. After this time, pentane is added and the organic layer is

washed with water (twice) and brine. The organic phase is dried over Na_2SO_4, concentrated *in vacuo* and purified by distillation to give **1a,b**.

Methyl 2-[(trimethylsilyl)oxy]acrylate (**1a**)[140]

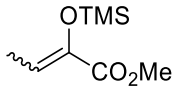


Starting from methyl pyruvate (5.11 g, 50 mmol) and TMSCl (7.10 g, 65 mmol) in DCM (50 mL), the product **1a** was isolated as a colorless oil (8.63 g, 99 %) after distillation (T = 53 °C, p = 15 mbar).

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.23 (s, 9H, $Si(CH_3)_3$), 3.77 (s, 3H, OCH_3), 4.88 (d, 1H, H_A-CH_2, $^2J_{H\text{-}H}$ = 1.2 Hz), 5.51 (d, 1H, H_B-CH_2, $^2J_{H\text{-}H}$ = 1.2 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = -0.1 ($Si(CH_3)_3$), 52.1 (OCH_3), 104.0 (CH_2), 146.9 (CCH_2), 164.9 (C=O).

Methyl 2-[(trimethylsilyl)oxy]but-2-enoate (**1b**)



Starting from methyl 2-oxobutanoate (1.74 g, 15 mmol) and TMSCl (2.68 g, 21 mmol) in DCM (15 mL), the product **1b** was isolated as a colorless oil (2.65 g, 94 %) after distillation (T = 74 °C, p = 30 mbar).

Anal. calcd for $C_8H_{16}O_3Si$: C, 51.03; H, 8.56. Found: C, 51.06; H, 8.59 %.

HRMS (ESI) calculated for $C_8H_{17}O_3Si$: 189.09415, found 189.09402.

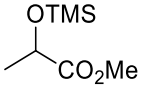
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.21 (s, 9H, $Si(CH_3)_3$), 1.70 (d, 3H, CH_3, $^3J_{H\text{-}H}$ = 7.1 Hz), 3.74 (s, 3H, OCH_3), 6.13 (d, 1H, CH, $^3J_{H\text{-}H}$ = 7.1 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 0.4 ($Si(CH_3)_3$), 11.3 (CH_3), 51.8 (OCH_3), 118.4 (CH), 141.3 (C-O), 165.2 (C=O).

General procedure for the synthesis of 2-[(trimethylsilyl)oxy] esters **2a,b**

The substrate (1.0 eq) and the Rh precatalyst (1 mol%) are transferred into a glass vial, which is placed into a stainless steel autoclave. The solvent (4 mL/1.0 mmol substrate) is added under an argon atmosphere and the autoclave is purged with argon (three times) followed by hydrogen (three times). The indicated reaction conditions (H_2-pressure, temperature and reaction time) are adjusted by an automatic program. After stirring for the adjusted time, the mixture is concentrated under reduced pressure. The enantiomeric excess is determined by GC analysis. A racemic mixture of **2b**, as sample for the quantitative and qualitative analysis, is prepared by the hydrogenation of **1b** with 10 % Pd/C in THF.

Methyl 2-[(trimethylsilyl)oxy]propanoate (**2a**)[141]



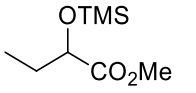
Anal. calcd for $C_7H_{16}O_3Si$: C, 47.69; H, 9.15. Found: C, 47.73; H, 9.26 %.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = -0.06 (s, 9H, $Si(CH_3)_3$), 1.14 (d, 3H, CH_3, $^3J_{H\text{-}H}$ = 6.8 Hz), 3.45 (s, 3H, OCH_3), 4.06 (q, 1H, CH, $^3J_{H\text{-}H}$ = 6.8 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = -0.1 ($Si(CH_3)_3$), 21.4 (CH_3), 51.7 (OCH_3), 68.2 (CH), 174.1 (C=O).

Separation of enantiomers by GC on Chiraldex β-PM (50 m×0.25 mm), 80/15-8-180; t_R = 10.5 min for (+)-enantiomer and t_R = 10.7 min for (–)-enantiomer.

Methyl 2-[(trimethylsilyl)oxy]butanoate (**2b**)



Anal. calcd for $C_8H_{18}O_3Si$: C, 50.49; H, 9.53. Found: C, 50.30; H, 9.51 %.

HRMS (ESI) calculated for $C_8H_{19}O_3Si$: 191.32060, found 191.32073.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.13 (s, 9H, $Si(CH_3)_3$), 0.93 (t, 3H, CH_3, $^3J_{H\text{-}H}$ = 7.2 Hz), 1.68-1.73 (m, 2H, CH_2), 3.72 (s, 3H, OCH_3), 4.11 (dd, 1H, CH, $^3J_{H\text{-}A}$ = 7.5 Hz, $^3J_{H\text{-}B}$ = 4.9 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 0.2 ($Si(CH_3)_3$), 10.4 (CH_3), 24.4 (CH_2), 51.9 (OCH_3), 68.5 (CH), 173.9 (C=O).

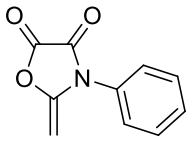
Separation of enantiomers by GC on Chiraldex β-PM (50 m×0.25 mm), 75/20-8-180; t_R = 17.0 min for (+)-enantiomer and t_R = 17.3 min for (–)-enantiomer.

5.1.2.2 Synthesis of *N*,*O*-acetals

General procedure for the synthesis of 2-methylene-3-substituted-oxazolidine-4,5-diones **3a,b**

The corresponding amide (1.0 eq) is dissolved in benzene (0.5 mL/1.0 mmol amide) and heated to 60 °C. Oxalyl chloride (1.08 eq) is added dropwise and the mixture is then refluxed for 24 h. After this time, it is cooled to room temperature and concentrated *in vacuo*. Kugelrohr distillation of the residue gives **3a,b**.

2-Methylene-3-phenyloxazolidine-4,5-dione (**3a**)



Starting from acetanilide (9.46 g, 70 mmol) and oxalyl chloride (9.52 g, 75 mmol) in benzene (35 mL), the product **3a** was isolated as a white solid (10.32 g, 78 %) after Kugelrohr distillation (*T* = 120-130 °C, *p* = 0.1 mbar).

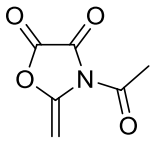
Anal. calcd for $C_{10}H_7NO_3$: C, 63.49; H, 3.73. Found: C, 63.30; H, 3.71 %.

HRMS (ESI) calculated for $C_{10}H_8NO_3$: 190.17487, found 190.17491.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 4.16 (d, 1H, H_A-CH_2, $^2J_{A\text{-}B}$ = 4.8 Hz), 4.53 (d, 1H, H_B-CH_2, $^2J_{A\text{-}B}$ = 4.8 Hz), 7.36-7.40 (m, 2H, CH-Ar), 7.48-7.60 (m, 3H, CH-Ar).

^{13}C NMR (63 MHz, $CDCl_3$): δ (ppm) = 75.5 (CH_2), 126.4 ($2CH_{Ar}$), 130.0 ($2CH_{Ar}$), 130.1 (CH_{Ar}), 130.9 (C_{Ar}), 147.2 (*C*CH_2), 149.8 (C=O), 154.1 (C=O).

3-Acetyl-2-methyleneoxazolidine-4,5-dione (**3b**)



Starting from diacetamide (5.06 g, 50 mmol) and oxalyl chloride (6.80 g, 54 mmol) in benzene (25 mL), the product **3b** was isolated as a white solid (6.00 g, 77 %) after Kugelrohr distillation (*T* = 120-140 °C, *p* = 0.2 mbar).

Anal. calcd for $C_6H_5NO_4$: C, 46.46; H, 3.25. Found: C, 46.30; H, 3.20 %.

HRMS (ESI) calculated for $C_6H_6NO_4$: 156.02914, found 156.02899.

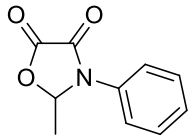
^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) = 2.70 (s, 1H, CH_3), 4.83 (d, 1H, H_A-CH_2, $^2J_{A\text{-}B}$ = 4.1 Hz), 5.56 (d, 1H, H_B-CH_2, $^2J_{A\text{-}B}$ = 4.2 Hz).

^{13}C NMR (63 MHz, $CDCl_3$): δ (ppm) = 26.2 (CH_3), 83.7 (CH_2), 142.1 (*C*CH_2), 150.4 (C=O), 152.8 (C=O), 167.7 (C=O).

General procedure for the asymmetric hydrogenation of 2-methylene-3-substituted-oxazolidine-4,5-diones **3a,b**

The substrate (1.0 eq) and Rh precatalyst (1 mol%) are transferred into a glass vial, which is placed into a stainless steel autoclave. The solvent (8 mL/1.0 mmol substrate) is added under an argon atmosphere and the autoclave is purged with argon (three times) followed by hydrogen (three times). The indicated reaction conditions (H_2-pressure, temperature and reaction time) are adjusted by an automatic program. After stirring for the adjusted time, the mixture is concentrated under reduced pressure. The enantiomeric excess is determined by GC analysis. Racemic mixtures of **4a,b**, as samples for the quantitative and qualitative analysis, are prepared by the hydrogenation of **3a,b** with 10 % Pd/C in THF.

2-Methyl-3-phenyloxazolidine-4,5-dione (**4a**)



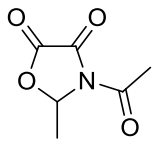
Anal. calcd for $C_{10}H_9NO_3$: C, 62.82; H, 4.74. Found: C, 62.92; H, 4.80 %.

HRMS (ESI) calculated for $C_{10}H_{10}NO_3$: 192.06552, found 192.06540.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.65 (d, 3H, CH_3, $^3J_{H\text{-}H}$ = 5.6 Hz), 6.20 (q, 1H, CH, $^3J_{H\text{-}H}$ = 5.6 Hz), 7.35-7.41 (m, 1H, CH-Ar), 7.45-7.53 (m, 4H, CH-Ar).

^{13}C NMR (63 MHz, $CDCl_3$): δ (ppm) = 20.7 (CH_3), 84.8 (CH), 122.2 ($2CH_{Ar}$), 128.2 (CH_{Ar}), 129.8 ($2CH_{Ar}$), 133.4 (C_{Ar}), 150.7 (C=O), 158.3 (C=O).

3-Acetyl-2-methyloxazolidine-4,5-dione (**4b**)



Anal. calcd for $C_6H_7NO_4$: C, 45.86; H, 4.49. Found: C, 46.02; H, 4.54 %.

HRMS (ESI) calculated for $C_6H_8NO_4$: 158.04478, found 158.04489.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.77 (d, 3H, CHC*H*$_3$, $^3J_{H\text{-}H}$ = 5.1 Hz), 2.64 (s, 3H, CH_3), 6.06 (q, 1H, CH, $^3J_{H\text{-}H}$ = 5.1 Hz).

^{13}C NMR (63 MHz, $CDCl_3$): δ (ppm) = 21.3 (CH*C*H$_3$), 24.8 (CH_3), 84.5 (CH), 151.5 (C=O), 157.0 (C=O), 169.0 (C=O).

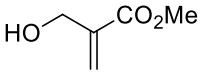
Separation of enantiomers by GC on CP-Chirasil-Dex CB (25 m×0.32 mm), isotherm 150 °C; t_R = 7.1 min for (+)-enantiomer and t_R = 8.5 min for (–)-enantiomer.

5.1.2.3 Synthesis of β^2-homoalanine derivatives and secondary products

General procedure for the synthesis of alkyl (2-hydroxymethyl)acrylates **5a,b**

Paraformaldehyde (1.0 eq), alkyl acrylate (3.0 eq) and DABCO (1.0 eq) are dissolved in dioxane:water (2 mL/1.0 mmol paraformaldehyde, *v*:*v* 1:1) and stirred at room temperature for 72 h. The mixture is dissolved in MTBE and the organic phase is separated, washed with water and brine (twice) and finally dried over Na_2SO_4. The organic layer is concentrated *in vacuo* and purified, if necessary, by column chromatography to give **5a,b**.

Methyl (2-hydroxymethyl)acrylate (**5a**)[142]

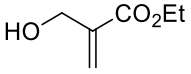


Starting from paraformaldehyde (9.0 g, 0.3 mol), methyl acrylate (77.5 g, 0.9 mol) and DABCO (33.7 g, 0.3 mol) in dioxane:H_2O (600 mL), the product was isolated as a white solid (15.0 g, 43 %) after column chromatography (cyclohexane/EtOAc = 4:1 to 2:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.32 (brs, 1H, OH), 3.80 (s, 3H, OCH_3), 4.33 (s, 2H, CH_2), 5.85 (s, 1H, H_A-CH_2), 6.25 (s, 1H, H_B-CH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 51.9 (OCH_3), 62.5 (OCH_2), 125.9 (CH_2), 139.3 (C), 166.8 (C=O).

Ethyl (2-hydroxymethyl)acrylate **5b**[142]

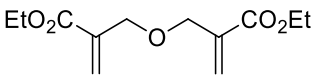


Starting from paraformaldehyde (9.0 g, 0.3 mol), ethyl acrylate (90.1 g, 0.9 mol) and DABCO (33.7 g, 0.3 mol) in dioxane:H_2O (600 mL) the product was isolated as a colorless liquid (28.0 g, 70 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.23 (t, 3H, CH_3, $^3J_{H\text{-}H}$ = 7.1 Hz), 3.11 (brs, 1H, OH), 4.15 (q, 2H, OCH_2, $^3J_{H\text{-}H}$ = 7.1 Hz), 4.24 (brs, 2H, OCH_2), 5.77 (m, 1H, H_A-CH_2), 6.17 (m, 1H, H_B-CH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 14.0 (CH_3), 60.7 (OCH_2), 61.8 (OCH_2), 125.1 (CH_2), 139.6 (C), 166.2 (C=O).

Diethyl 2,2'-oxybis(methylene)diacrylate (**5b'**)



Next to ethyl (2-hydroxymethyl)acrylate **5b**, the formation of diethyl 2,2'-oxybis(methylene)diacrylate **5b'** could be observed as a side product (ca. 9 mol%); this can be cleaved into two molecules of **1b** under acidic conditions in the next step.

HRMS (ESI) calculated for $C_{12}H_{19}O_5$ 243.1227, found 243.12252.

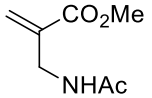
HRMS (ESI) calculated for $C_{12}H_{18}NaO_5$ 265.10464, found 265.10492.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.22 (t, 6H, $2CH_3$, $^3J_{H\text{-}H}$ = 7.1 Hz), 4.14 (q, 4H, $2OCH_2$, $^3J_{H\text{-}H}$ = 7.1 Hz), 4.15 (s, 4H, $2OCH_2$), 5.82 (m, 2H, $2H_A$-CH_2), 6.24 (m, 2H, $2H_B$-CH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 14.0 ($2CH_3$), 60.6 ($2OCH_2$), 68.7 ($2OCH_2$), 125.6 ($2CH_2$), 137.0 (2C), 165.7 (2C=O).

Procedure for the synthesis of methyl (2-acetamidomethyl)acrylate (**6a**)

Methyl (2-hydroxymethyl)acrylate **5a** (7.0 g, 60.3 mmol) is dissolved in acetonitrile (250 mL) and the solution was stirred at 60 °C. Methanesulfonic acid (162 mL, 2.5 mol) is dropped into the solution within 15 min. The reaction mixture is then heated to 110 °C and stirred for additional 6 h at this temperature. The solution is cooled to 0 °C and diluted in water. The pH-value is adjusted to 7-8 by adding solid K_2CO_3. After extraction with diethyl ether (2×100 mL), the organic phase is washed with brine (50 mL) and dried over Na_2SO_4. The organic layer is concentrated *in vacuo* and purified by flash chromatography (cyclohexane/EtOAc = 4:1 to 2:1) to yield **6a** as a white solid (4.50 g, 47 %).



Anal. calcd for $C_7H_{11}NO_3$: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.73; H, 6.97; N, 8.99 %.

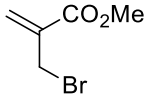
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.95 (t, 3H, CH_3) 3.74 (s, 3H, OCH_3), 4.04 (brd, 2H, NCH_2, $^3J_{H\text{-}H}$ = 6.1 Hz), 5.78 (m, 1H, H_A-CH_2), 6.22 (brs, 1H, NH), 6.22 (m, 1H, H_B-CH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 23.2 (CH_3), 40.5 (NCH_2), 51.9 (OCH_3), 127.1 (CH_2), 136.4 (C), 166.7 (C=O), 169.9 (C=O).

General procedure for the synthesis of alkyl (2-bromomethyl)acrylates **7a,b**

Alkyl (2-hydroxymethyl)acrylate **5a,b** (2.0 eq) is dissolved in diethyl ether (1 mL/1.0 mmol substrate) and phosphorus tribromide (1.0 eq) is added slowly at 0 °C via syringe to the stirred solution. The mixture is heated to room temperature and stirred for further 2 h. After cooling to 0 °C, water is slowly added. The crude product is extracted with diethyl ether (three times), the combined organic phases are washed with brine (twice) and dried over Na_2SO_4. The organic layer is concentrated *in vacuo* and purified, if necessary, by Kugelrohr disitillation to give **7a,b**.

Methyl (2-bromomethyl)acrylate (**7a**)[96a]

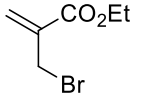


Starting from methyl (2-hydroxymethyl)acrylate **5a** (18.58 g, 160 mmol) and PBr_3 (21.65 g, 80 mmol) in Et_2O (80 mL), the product **7a** was isolated as a yellowish liquid and used without further purification (12.80 g, 89 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.75 (s, 3H, OCH_3), 4.12 (s, 2H, CH_2Br), 5.91 (1H, m, H_A-CH_2), 6.27 (1H, m, H_B-CH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 29.2 (CH_2Br), 52.1 (OCH_3), 129.1 (CH_2), 137.1 (C), 165.1 (C=O).

Ethyl (2-bromomethyl)acrylate (**7b**)[96b]



Starting from ethyl (2-hydroxymethyl)acrylate **5b** (20.82 g, 160 mmol) and PBr_3 (21.65 g, 80.0 mmol) in Et_2O (80 mL), the product **7b** was isolated as a colorless liquid after Kugelrohr distillation (10.30 g, 67 %, T = 81-84 °C, p = 4 mbar).

Anal. calcd for $C_6H_9BrO_2$: C, 37.33; H, 4.70; Br, 41.39. Found: C, 37.33; H, 4.53; Br, 41.67 %.

MS (EI, 70 eV, *m*/*z*): 194 $[M+2]^+$, 14; 192 $[M]^+$, 14; 166 $[M+2\text{-}C_2H_4]^+$, 97; 164 $[M\text{-}C_2H_4]^+$, 97; 149 $[M+2\text{-}C_2H_5O]^+$, 62; 147 $[M\text{-}C_2H_5O]^+$, 62; 113 $[M\text{-}Br]^+$, 58; 39 $[C_3H_3]^+$, 100.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.29 (t, 3H, CH_3, $^3J_{H\text{-}H}$ = 7.2 Hz), 4.15 (d, 2H, CH_2Br, $J_{H\text{-}H}$ = 0.8 Hz), 4.23 (q, 2H, OCH_2, $^3J_{H\text{-}H}$ = 7.2 Hz), 5.91 (m, 1H, H_A-CH_2), 6.29 (m, 1H, H_B-CH_2).

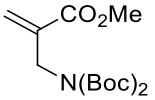
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 14.1 (CH_3), 29.3 (CH_2Br), 61.2 (OCH_2) 128.9 (CH_2), 137.5 (C), 164.7 (C=O).

General procedure for the synthesis of alkyl 2-{[bis(*tert*-butoxycarbonyl)amino]methyl}acrylates **6b,c**

Alkyl (2-bromomethyl)acrylate **7a,b** (1.0 eq) is added in one portion to a suspension of di-*tert*-butyl iminodicarboxylate (1.0 eq) and K_2CO_3 (1.5 eq) in acetonitrile (1 mL/1.0 mmol substrate). The mixture is stirred at room temperature for 72 h. The solution is treated with brine and extracted with

ethyl acetate (three times). The combined organic phases are washed with water and dried over Na_2SO_4. The organic layer is concentrated *in vacuo* to give **6b,c**.

Methyl 2-{[bis(*tert*-butoxycarbonyl)amino]methyl}acrylate (**6b**)[97a]



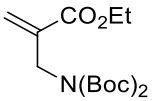
Starting from methyl (2-bromomethyl)acrylate **5a** (4.42 g, 24.7 mmol), Boc_2NH (5.37 g, 24.7 mmol) and K_2CO_3 (5.12 g, 37.1 mmol) in MeCN (25 mL), the product **6b** was isolated without further purification as an off-white solid (7.40 g, 95 %, mp 68-69 °C).

Anal. calcd for $C_{15}H_{25}NO_6$: C, 57.13; H, 7.99; N, 4.44. Found: C, 57.07; H, 7.76; N, 4.24 %.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.44 (s, 18H, $2C(CH_3)_3$), 3.73 (s, 3H, CH_3), 4.41 (t, 2H, NCH_2, $J_{H\text{-}H}$ = 1.8 Hz), 5.52 (m, 1H, H_A-CH_2), 6.23 (m, 1H, H_B-CH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 27.9 ($2C(CH_3)_3$), 46.1 (NCH_2), 51.8 (CH_3), 82.6 ($2C(CH_3)_3$), 123.4 (CH_2), 136.6 (C), 152.1 (2C=O), 166.1 (C=O).

Ethyl 2-{[bis(*tert*-butoxycarbonyl)amino]methyl}acrylate (**6c**)



Starting from ethyl (2-bromomethyl)acrylate **5b** (4.73 g, 24.5 mmol), Boc_2NH (5.33 g, 24.5 mmol) and K_2CO_3 (5.08 g, 36.8 mmol) in MeCN (25 mL), the product **6c** was isolated without further purification as a colorless oil (8.00 g, 99 %).

Anal. calcd for $C_{16}H_{27}NO_6$: C, 58.34; H, 8.26; N, 4.25. Found: C, 58.06; H, 8.02; N, 4.05 %.

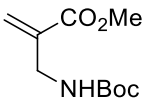
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.27 (t, 3H, CH_3, $^3J_{H\text{-}H}$ = 7.2 Hz); 1.44 (s, 18H, $2C(CH_3)_3$), 4.19 (q, 2H, OCH_2, $^3J_{H\text{-}H}$ = 7.2 Hz), 4.42 (t, 2H, NCH_2, $J_{H\text{-}H}$ = 1.8 Hz), 5.50 (m, 1H, H_A-CH_2), 6.22 (m, 1H, H_B-CH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 14.1 (CH_3), 27.9 ($2C(CH_3)_3$), 46.1 (NCH_2), 60.7 (OCH_2), 82.6 ($2C(CH_3)_3$), 122.9 (CH_2), 136.9 (C), 152.1 (2C=O), 165.7 (C=O).

General procedure for the synthesis of alkyl 2-{[(*tert*-butoxycarbonylamino]methyl}acrylate **6d,e**

N-Diprotected acrylate **6b,c** (1.0 eq) is dissolved in tetrahydrofuran (5 mL/1.0 mmol substrate) and scandium triflate (0.1 eq) is added in one portion. After stirring at room temprature for 3 h, the mixture is concentrated *in vacuo* and ethyl acetate is added. The organic phase is washed with water and dried over Na_2SO_4. The organic layer is concentrated *in vacuo* and purified by flash chromatography to give **6d,e**.

Methyl 2-{[(*tert*-butoxycarbonyl)amino]methyl}acrylate (**6d**)[97a]



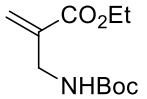
Starting from methyl 2-{[bis(*tert*-butoxycarbonyl)amino]methyl}acrylate **6b** (6.31 g, 20.0 mmol) and $Sc(OTf)_3$ (984 mg, 2.0 mmol) in THF (100 mL), the product **6d** was isolated as a pale yellow oil (3.60 g, 84 %) after column chromatography (cyclohexane/EtOAc = 4:1).

Anal. calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51. Found: C, 55.54; H, 7.72; N, 6.31 %.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.37 (s, 9H, $C(CH_3)_3$), 3.70 (s, 3H, s, CH_3), 3.88 (brd, 2H, NCH_2, $^3J_{H\text{-}H}$ = 6.3 Hz), 5.05 (brs, 1H, NH), 5.72 (m, 1H, H_A-CH_2) 6.18 (m, 1H, H_B-CH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 28.2 (C(CH_3)$_3$), 41.5 (NCH_2), 51.8 (OCH_3), 79.3 (C(CH_3)$_3$), 126.2 (CH_2), 137.0 (C), 155.6 (C=O), 166.5 (C=O).

Ethyl 2-{[(*tert*-butoxycarbonylamino]methyl}acrylate (**6e**)[143]



Starting from ethyl 2-{[bis(*tert*-butoxycarbonyl)amino]methyl}acrylate **6c** (6.59 g, 20.0 mmol) and $Sc(OTf)_3$ (984 mg, 2.0 mmol) in THF (100 mL), the product **6e** was isolated as a pale yellow oil (3.90 g, 84 %) after column chromatography (cyclohexane/EtOAc = 19:1 to 9:1).

Anal. calcd for $C_{11}H_{19}NO_4$: C, 57.63; H, 8.35; N, 6.11. Found: C, 57.79; H, 8.13; N, 5.91 %.

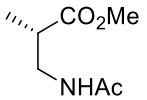
^{1}H NMR ($CDCl_3$): δ (ppm) = 1.26 (t, 3H, CH_3, $^3J_{H\text{-}H}$ = 7.1 Hz,), 1.39 (s, 9H, C(CH_3)$_3$), 3.91 (brd, 2H, NCH_2, $^3J_{H\text{-}H}$ = 6.1 Hz), 4.17 (q, 2H, OCH_2, $^3J_{H\text{-}H}$ = 7.1 Hz), 5.01 (brs, 1H, NH), 5.71 (m, 1H, H_A-CH_2), 6.19 (m, 1H, H_B-CH_2).

^{13}C NMR ($CDCl_3$): δ (ppm) = 14.1 (CH_3), 28.3 (C(CH_3)$_3$), 41.5 (NCH_2), 60.7 (OCH_2) 79.4 (C(CH_3)$_3$), 125.9 (CH_2), 137.3 (C), 155.6 (C=O), 166.1 (C=O).

General procedure for the asymmetric hydrogenation of dehydro β^2-amino acrylates **6a-e**

The substrate (1.0 eq) and Rh precatalyst (1 mol%) are transferred into a glass vial, which is placed into a stainless steel autoclave. The solvent (12 mL/1.0 mmol substrate) is added under an argon atmosphere and the autoclave is purged with argon (three times) followed by hydrogen (three times). The indicated reaction conditions (H_2-pressure, temperature and reaction time) are adjusted by an automatic program. After stirring for the adjusted time, the mixture is concentrated under reduced pressure. The enantiomeric excess is determined by HPLC or GC analysis. Racemic mixtures of **8a-e**, as samples for the quantitative and qualitative analysis, are prepared by the hydrogenation of **6a-e** with 10 % Pd/C in methanol.

(*S*)-Methyl-3-acetamido-2-methylpropanoate (**8a**)



$[\alpha]_D^{24}$ = +45.5 (*c* 1.00, $CHCl_3$), >99 %ee.

HRMS (ESI) calculated for $C_7H_{14}NO_3$ 160.09682, found 160.09691.

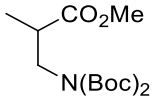
HRMS (ESI) calculated for $C_7H_{13}NO_3Na$ 182.07876, found 182.07909.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.14 (d, 3H, CHCH_3, $^3J_{H\text{-}H}$ = 7.2 Hz), 1.93 (s, 3H, CH_3), 2.67 (m, 1H, C$H$$CH_3$), 3.24 (m, 1H, H_A-NCH_2), 3.46 (m, 1H, H_B-NCH_2), 3.67 (s, 3H, OCH_3), 6.21 (brs, 1H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 14.8 (CH_3), 23.2 (CH_3), 39.4 (NCH_2), 41.6 (CHCH$_3$), 51.9 (OCH_3), 170.3 (C=O), 176.0 (C=O).

Separation of enantiomers by GC on Lipodex E (25 m×0.25 mm), 100/30-8-180/10; t_R = 15.1 min for (+)-enantiomer and t_R = 16.6 min for (–)-enantiomer. The assignment of absolute configuration to the GC-peaks was determined by deprotection of (*S*)-**8d** and subsequent *N*-acetylation to (*S*)-**8a**.

Methyl 3-[bis(*tert*-butoxycarbonyl)amino]-2-methylpropanoate (**8b**)



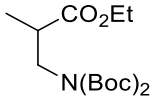
HRMS (ESI) calculated for $C_{15}H_{27}NNaO_6$ 340.17306, found 340.17298.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.08 (d, 3H, CHC*H*$_3$, $^3J_{H\text{-}H}$ = 6.8 Hz), 1.44 (s, 18H, 2C$(CH_3)_3$), 2.78 (m, 1H, C*H*CH_3), 3.58 (dd, 1H, H_A-NCH_2, $^2J_{A\text{-}B}$ = 14.1 Hz, $^3J_{H\text{-}A}$ = 6.8 Hz), 3.60 (s, 3H, OCH_3), 3.81 (dd, 1H, H_B-NCH_2, $^2J_{A\text{-}B}$ = 14.1 Hz, $^3J_{H\text{-}B}$ = 7.6 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 14.5 (CH*C*H_3), 27.9 (2C(*C*$H_3)_3$), 39.1 (*C*HCH_3), 48.6 (NCH_2), 51.6 (OCH_3), 82.4 (2*C*$(CH_3)_3$), 152.4 (2C=O), 175.0 (C=O).

Separation of enantiomers by HPLC on AD-H (150×4.6 mm), heptane/EtOH = 95:5, rate = 0.5 mL/min; t_R = 7.1 min for (–)-enantiomer and t_R = 7.8 min for (+)-enantiomer.

Ethyl 3-[bis(*tert*-butoxycarbonyl)amino]-2-methylpropanoate (**8c**)



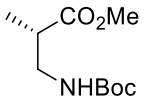
HRMS (ESI) calculated for $C_{16}H_{27}NNaO_6$ 352.17306, found 352.17298.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.09 (d, 3H, CHC*H*$_3$, $^3J_{H\text{-}H}$ = 7.2 Hz), 1.19 (t, 3H, CH_3, $^3J_{H\text{-}H}$ = 7.2 Hz), 1.45 (s, 18H, 2C$(CH_3)_3$), 2.77 (m, 1H, C*H*CH_3), 3.59 (dd, 1H, H_A-CH_2, $^2J_{A\text{-}B}$ = 14.1 Hz, $^3J_{H\text{-}A}$ = 7.1 Hz), 3.81 (dd, 1H, H_B-CH_2, $^2J_{A\text{-}B}$ = 14.1 Hz, $^3J_{H\text{-}B}$ = 7.4 Hz), 4.05 (q, 2H, OCH_2, $^3J_{H\text{-}H}$ = 7.2 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 14.0 (CH_3), 14.5 (CH*C*H_3), 27.9 (2C(*C*$H_3)_3$), 39.0 (*C*HCH_3), 48.6 (NCH_2), 60.4 (OCH_2), 82.4 (2*C*$(CH_3)_3$), 152.4 (2C=O), 174.6 (C=O).

Separation of enantiomers by HPLC on Reprosil 100 (250×4.6 mm), heptane/EtOH = 99:1, rate = 0.5 mL/min; t_R = 24.5 min for (–)-enantiomer and t_R = 28.0 min for (+)-enantiomer.

(*S*)-Methyl 3-[(*tert*-butoxycarbonyl)amino]-2-methylpropanoate (**8d**)[144]



$[\alpha]_D^{22}$ = +23.3 (*c* 1.20, $CHCl_3$), 94 %ee.

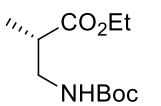
HRMS (ESI) calculated for $C_{10}H_{19}NO_4Na$ 240.12063, found 240.12080.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.12 (d, 3H, CHC*H*$_3$, $^3J_{H\text{-}H}$ = 7.2 Hz), 1.39 (s, 9H, C$(CH_3)_3$), 2.63 (m, 1H, C*H*CH_3), 3.15-3.32 (m, 2H, NCH_2), 3.65 (s, 3H, OCH_3), 4.96 (brs, 1H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 14.6 (CH*C*H_3), 28.3 (C(*C*$H_3)_3$), 39.9 (*C*HCH_3), 42.9 (NCH_2), 51.7 (OCH_3), 79.2 (*C*$(CH_3)_3$), 155.9 (C=O), 175.7 (C=O).

Separation of enantiomers by GC on Chiraldex β-PM (50 m×0.25 mm), 110/22-8-180; t_R = 31.5 min for (+)-enantiomer and t_R = 31.7 min for (–)-enantiomer.

(*S*)-Ethyl 3-[(*tert*-butoxycarbonyl)amino]-2-methylpropanoate (**8e**)



$[\alpha]_D^{22}$ = +20.3 (*c* 1.00, $CHCl_3$), 96 %ee; $[\alpha]_D^{23}$ = +27.1 (*c* 1.00, MeOH), 96 %ee.

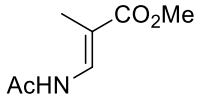
HRMS (ESI) calculated for $C_{11}H_{21}NO_4Na$ 254.13628, found 254.13655.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.13 (d, 3H, CHC*H*$_3$, $^3J_{H\text{-}H}$ = 7.2 Hz), 1.22 (t, 3H, CH_3, $^3J_{H\text{-}H}$ = 7.2 Hz), 1.39 (s, 9H, C$(CH_3)_3$), 2.62 (m, 1H, C*H*CH_3), 3.15-3.33 (m, 2H, NCH_2), 4.11 (q, 2H, OCH_2, $^3J_{H\text{-}H}$ = 7.2 Hz), 4.93 (brs, 1H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 14.1 (CH_3), 14.6 ($CHCH_3$), 28.3 ($C(CH_3)_3$), 39.9 ($CHCH_3$), 42.9 (NCH_2), 60.5 (OCH_2), 79.2 ($C(CH_3)_3$), 155.9 (C=O), 175.4 (C=O).

Separation of enantiomers by GC on Lipodex E (25 m×0.25 mm), 90/40-8-180/10; t_R = 43.8 min for (+)-enantiomer and t_R = 44.1 min for (–)-enantiomer.

(*E*)-Methyl 3-acetamido-2-methylacrylate ((*E*)-**9a**)

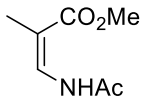


In some cases, (*E*)-methyl 3-acetamido-2-methylacrylate (*E*)-**9a** was visible as a side product in the final mixture after the hydrogenation of **6a**.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.76 (d, 3H, CCH_3, $^4J_{H\text{-}H}$ = 1.4 Hz), 2.10 (s, 3H, CH_3), 3.66 (s, 3H, OCH_3), 7.94 (brd, 1H, NCH, $^3J_{H\text{-}H}$ = 11.9 Hz), 8.43 (brs, 1H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 10.6 (CCH_3), 23.1 (CH_3), 51.4 (OCH_3), 107.3 (CCH_3), 132.2 (NCH), 168.4 (C=O), 168.5 (C=O).

(*Z*)-Methyl 3-acetamido-2-methylacrylate ((*Z*)-**9a**)

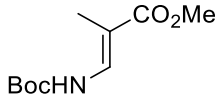


In some cases, (*Z*)-methyl 3-acetamido-2-methylacrylate (*Z*)-**9a** was visible as a side product in the final mixture after the hydrogenation of **6a**.

^{1}H NMR ($CDCl_3$): δ (ppm) = 1.77 (d, 3H, CCH_3, $^4J_{H\text{-}H}$ = 1.4 Hz), 2.06 (s, 3H, CH_3), 3.70 (s, 3H, OCH_3), 7.29 (brd, 1H, NCH, $^3J_{H\text{-}H}$ = 11.0 Hz), 10.30 (brs, 1H, NH).

^{13}C NMR ($CDCl_3$): δ (ppm) = 15.8 (CCH_3), 23.5 (CH_3), 51.4 (OCH_3), 104.3 (CCH_3), 134.6 (NCH), 168.1 (C=O), 168.9 (C=O).

(*E*)-Methyl 3-[(*tert*-butoxycarbonyl)amino]-2-methylacrylate ((*E*)-**9d**)

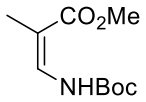


In some cases, (*E*)-methyl 3-[(*tert*-butoxycarbonyl)amino]-2-methylacrylate (*E*)-**9d** was visible as a side product in the final mixture after the hydrogenation of **6d**.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.47 (s, 9H, $C(CH_3)_3$), 1.73 (d, 3H, CCH_3, $^4J_{H\text{-}H}$ = 1.3 Hz), 3.68 (s, 3H, OCH_3), 6.60 (brd, 1H, NCH, $^3J_{H\text{-}H}$ = 11.4 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 10.1 (CCH_3), 28.3 ($C(CH_3)_3$), 51.3 (OCH_3), 81.9 ($C(CH_3)_3$), 104.8 (CCH_3), 134.2 (NCH), 151.8 (C=O), 168.7 (C=O).

(*Z*)-Methyl 3-[(*tert*-butoxycarbonyl)amino]-2-methylacrylate ((*Z*)-**9d**)

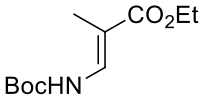


In some cases, (*Z*)-methyl 3-[(*tert*-butoxycarbonyl)amino]-2-methylacrylate (*Z*)-**9d** was visible as a side product in the final mixture after the hydrogenation of **6d**.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.43 (s, 9H, $C(CH_3)_3$), 1.76 (d, 3H, CCH_3, $^4J_{H\text{-}H}$ = 1.3 Hz), 3.70 (s, 3H, OCH_3), 7.09 (brd, 1H, NCH, $^3J_{H\text{-}H}$ = 11.4 Hz).

^{13}C NMR spectrum could not be analyzed due to the small amount in the final reaction mixture.

(*E*)-Ethyl 3-[(*tert*-butoxycarbonyl)amino]-2-methylacrylate ((*E*)-**9e**)

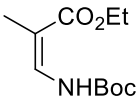


In some cases, (*E*)-Ethyl 3-[(*tert*-butoxycarbonyl)amino]-2-methylacrylate (*E*)-**9e** was visible as a side product in the final mixture after the hydrogenation of **4e**.

^{1}H NMR (300 MHz, CD_3OD): δ (ppm) = 1.28 (t, 3H, CH_3, $^3J_{H\text{-}H}$ = 7.1 Hz), 1.51 (s, 9H, $C(CH_3)_3$), 1.81 (d, 3H, CCH_3, $^4J_{H\text{-}H}$ = 1.2 Hz), 4.16 (q, 2H, OCH_2, $^3J_{H\text{-}H}$ = 7.1 Hz), 7.76 (brd, 1H, NCH, $^3J_{H\text{-}H}$ = 11.3 Hz).

^{13}C NMR spectrum could not be analyzed due to its small amount in the final reaction mixture.

(*Z*)-Ethyl 3-[(*tert*-butoxycarbonyl)amino]-2-methylacrylate ((*Z*)-**9e**)



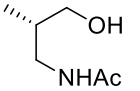
In some cases, (*Z*)-Ethyl 3-[(*tert*-butoxycarbonyl)amino]-2-methylacrylate (*Z*)-**9e** was visible as a side product in the final mixture after the hydrogenation of **6e**.

^{1}H NMR (300 MHz, CD_3OD): δ (ppm) = 1.29 (t, 3H, CH_3, $^3J_{H\text{-}H}$ = 7.1 Hz), 1.40 (s, 9H, $C(CH_3)_3$), 1.76 (d, 3H, CCH_3, $^4J_{H\text{-}H}$ = 1.2 Hz), 4.16 (q, 2H, OCH_2, $^3J_{H\text{-}H}$ = 7.1 Hz), 6.92 (brs, 1H, NCH).

^{13}C NMR spectrum could not be analyzed due to its small amount in the final reaction mixture.

Procedure for the synthesis of (*S*)-*N*-(3-hydroxy-2-methylpropyl)acetamide (**10a**)

(*S*)-Methyl 3-acetamido-2-methylpropanoate **8a** (318 mg, 2.0 mmol, >99 %ee) is dissolved in tetrahydrofuran (15 mL) and $LiAlH_4$ (228 mg, 6.0 mmol) is added slowly at 0 °C. The solution is stirred at room temperature for 2 h and then quenched with water (0.3 mL), 2 M NaOH (0.3 mL) and finally water (0.9 mL) again. The resulting white precipitate is filtered off and washed several times with dichloromethane. The combined organic phases are dried over Na_2SO_4 and then concentrated *in vacuo*. Column chromatography (EtOAc) yields **10a** as a pale yellow oil (150 mg, 57 %).



$[\alpha]_D^{24}$ = +21.6 (*c* 1.00, $CHCl_3$), 98 %ee.

HRMS (ESI) calculated for $C_6H_{14}NO_2$ 132.10191, found 132.10210.

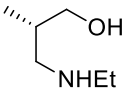
HRMS (ESI) calculated for $C_6H_{13}NO_2Na$ 154.08385, found 154.08407.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.83 (d, 3H, $CHCH_3$, $^3J_{H\text{-}H}$ = 7.0 Hz), 1.75 (m, 1H, $CHCH_3$), 3.06 (m, 1H, H_A-NCH_2), 3.25 (dd, 1H, H_B-NCH_2, $^2J_{A\text{-}B}$ = 11.5 Hz, $^3J_{H\text{-}B}$ = 7.1 Hz), 3.30 (m, 1H, H_A-OCH_2), 3.48 (dd, 1H, H_B-OCH_2, $^2J_{A\text{-}B}$ = 11.5 Hz, $^3J_{H\text{-}B}$ = 4.3 Hz), 3.78 (brs, 1H, OH), 6.85 (brs, 1H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 14.5 ($CHCH_3$), 22.8 ($C(CH_3)_3$), 35.6 ($CHCH_3$), 42.1 (NCH_2), 64.4 (OCH_2), 171.9 (C=O).

Separation of enantiomers by GC on Lipodex E (25 m×0.25 mm), 100/30-8-180/10; t_R = 39.0 min for (+)-enantiomer and t_R = 39.2 min for (–)-enantiomer.

(*S*)-3-(Ethylamino)-2-methylpropan-1-ol (**10a'**)



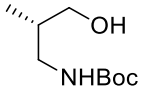
When the reaction time was extended by further 2 h at room temperature, the reduction of the acetyl group became visible in the NMR spectra of the crude mixture and thus the formation of (*S*)-3-(ethylamino)-2-methylpropan-1-ol **10a'** (ca. 11 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.75 (d, 3H, CHC*H*$_3$, $^3J_{H\text{-}H}$ = 6.9 Hz), 1.03 (t, 3H, $^3J_{H\text{-}H}$ = 7.2 Hz, CH_3), 1.89 (m, 1H, C*H*CH_3), 2.48-2.67 (m, 4H, CH_2NCH_2), 2.80 (m, 1H, H_A-OCH_2), 3.62 (m, 1H, H_B-OCH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 14.8 (CH*C*H_3), 14.8 (CH_3), 33.8 (*C*HCH_3), 44.0 (NCH_2), 55.7 (NCH_2), 70.3 (OCH_2).

Procedure for the synthesis of (*S*)-*tert*-butyl (3-hydroxy-2-methylpropyl)carbamate (**10b**)[145]

Ethyl 3-[(*tert*-butoxycarbonyl)amino]-2-methylpropanoate **8e** (694 mg, 3.0 mmol, 96 %ee) is dissolved in tetrahydrofuran (30 mL) and $LiAlH_4$ (342 mg, 9.0 mmol) is added slowly at 0 °C. The solution is stirred at this temperature for 1 h, warmed to room temperature and stirred for additional 4 h. The reaction mixture is then quenched with water (0.35 mL), 2 M NaOH (0.35 mL) and finally water (1 mL) again. The resulting white precipitate is filtered off and washed several times with dichloromethane. The combined organic phases are dried over Na_2SO_4 and then concentrated *in vacuo*. Column chromatography (cyclohexane/EtOAc = 4:1 to 1:1) yields **10b** as a colorless oil (400 mg, 69 %). Enantiomeric excess is determined by derivatization to **13**.



$[\alpha]_D^{23}$ = +13.7 (*c* 1.00, $CHCl_3$), 95 %ee.

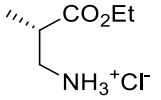
HRMS (ESI) calculated for $C_9H_{19}NO_3Na$ 212.12571, found 212.12573.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.83 (d, 3H, CHC*H*$_3$, $^3J_{H\text{-}H}$ = 7.0 Hz), 1.39 (s, 9H, $C(CH_3)_3$), 1.72 (m, 1H, C*H*CH_3), 2.99 (dd, 1H, H_A-OCH_2, $^2J_{A\text{-}B}$ = 14.2 Hz, $^3J_{H\text{-}A}$ = 6.8 Hz), 3.19 (dd, 1H, H_B-OCH_2, $^2J_{A\text{-}B}$ = 14.2 Hz, $^3J_{H\text{-}B}$ = 3.8 Hz), 3.30 (dd, 1H, H_A-NCH_2, $^2J_{A\text{-}B}$ = 11.6 Hz, $^3J_{H\text{-}A}$ = 7.0 Hz), 3.50 (dd, 1H, H_B-NCH_2, $^2J_{A\text{-}B}$ = 11.6 Hz, $^3J_{H\text{-}B}$ = 4.4 Hz), 3.50 (brs, 1H, OH), 4.93 (brs, 1H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 14.3 (CH*C*H_3), 28.3 (C(*C*H_3)$_3$), 36.2 (*C*HCH_3), 42.7 (NCH_2), 64.4 (OCH_2), 79.6 (*C*$(CH_3)_3$), 157.3 (C=O).

Procedure for the synthesis of (*S*)-ethyl 3-amino-2-methylpropanoate hydrochloride (**11**)

To ethyl 3-[(*tert*-butoxycarbonyl)amino]-2-methylpropanoate **8e** (1.30 g, 5.6 mmol, 96 %ee) is added a solution of 4 M $HCl_{(g)}$ in dioxane at room temperature. After stirring for 2 h, the solution is concentrated *in vacuo* to yield the crude hydrochloride **11** as a colorless thick syrup (750 mg, 80 %). An enantiomeric excess of 96% was determined by GC analysis after derivatization to the *N*-Boc-derivative **8e** by addition of 3.0 eq of Boc_2O/Et_3N to a solution of **11** in dichloromethane.



$[\alpha]_D^{23}$ = +11.4 (*c* 0.56, MeOH), 96%ee.

HRMS (ESI) calculated for $C_6H_{14}NO_2$ 132.10191, found 132.1021.

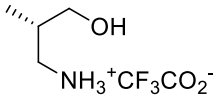
HRMS (ESI) calculated for $C_6H_{13}NNaO_2$ 154.08385, found 154.08407.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.23 (t, 3H, CH_3, $^3J_{H\text{-}H}$ = 7.0 Hz), 1.27 (d, 3H, CHC*H*$_3$, $^3J_{H\text{-}H}$ = 7.0 Hz) 2.95-3.35 (m, 3H, C*H*CH_3 and NCH_2), 4.15 (q, 2H, OCH_2, $^3J_{H\text{-}H}$ = 7.0 Hz), 6.48 (brs, 1H, OH), 8.10 (brs, 1H, NH_3^+).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 14.0 (CH_3), 15.1 (CH*C*H_3), 37.1 (*C*HCH_3), 41.9 (NCH_2), 61.4 (OCH_2), 174.0 (C=O).

Procedure for the synthesis of (*S*)-3-amino-2-methylpropan-1-ol trifluoroacetate (**12**)

To a solution of (*S*)-*tert*-butyl (3-hydroxy-2-methylpropyl)carbamate **10b** (189 mg, 1.0 mmol) in dichloromethane (5 mL) is added trifluoroacetic acid (1.5 mL). The solution is stirred at room temperature for 3 h and then concentrated *in vacuo*. The crude product **12** is isolated as a colorless, viscous oil (164 mg, 81 %).



$[\alpha]_D^{23}$ = -8.2 (*c* 1.00, MeOH).

Anal. calcd for $C_6H_{12}F_3NO_3$: C, 35.47; H, 5.95; F, 28.05; N, 6.89. Found: C, 35.75; H, 5.60; F, 27.87; N, 6.66 %.

HRMS (ESI) calculated for $C_4H_{12}NO^+$ 90.09134, found 90.09184.

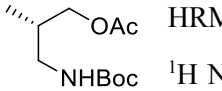
^{19}F NMR (282 MHz, CD_3OD): δ (ppm) = -76.5 (s).

^{1}H NMR (300 MHz, CD_3OD): δ (ppm) = 0.97 (d, 3H, CHCH_3, $^3J_{H\text{-}H}$ = 6.9 Hz), 2.00 (m, 1H, CHCH$_3$), 2.85 (dd, 1H, H_A-NCH$_2$, $^2J_{A\text{-}B}$ = 12.7 Hz, $^3J_{H\text{-}A}$ = 6.0 Hz), 3.00 (dd, 1H, H_B-NCH$_2$, $^2J_{A\text{-}B}$ = 12.7 Hz, $^3J_{H\text{-}B}$ = 7.6 Hz), 3.64 (dd, 1H, H_A-OCH$_2$, $^2J_{A\text{-}B}$ = 10.8 Hz, $^3J_{H\text{-}A}$ = 7.8 Hz), 3.64 (dd, 1H, H_B-OCH$_2$, $^2J_{A\text{-}B}$ = 10.8 Hz, $^3J_{H\text{-}B}$ = 4.6 Hz).

^{13}C NMR (75 MHz, CD_3OD): δ (ppm) = 14.4 (CHCH$_3$), 35.0 (CHCH$_3$), 45.0 (NCH$_2$), 66.6 (OCH$_2$), 118.2 (q, CF$_3$, $J_{C\text{-}F}$ = 287 Hz), 162.9 (q, C=O, $J_{C\text{-}F}$ = 38.0 Hz).

Procedure for the synthesis of (*S*)-3-[(*tert*-butoxycarbonyl)amino]-2-methylpropyl acetate (**13**)

Racemic alcohol **10b** (75 mg, 0.4 mmol) is dissolved in dichloromethane (2 mL) and the mixture is cooled to 0 °C. Triethylamine (60 mg, 0.6 mmol) and then acetyl chloride (39 mg, 0.5 mmol) are added at 0 °C. The mixture is stirred for 1 h, warmed to room temperature and stirred for further 2 h. The solution is then concentrated *in vacuo* and the residue is purified by chromatography (cyclohexane/EtOAc = 4:1) to yield **13** (40 mg, 46 %) as a colorless oil.



HRMS (ESI) calculated for $C_{11}H_{21}NO_4Na$ 254.13628, found 254.13605.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.91 (d, 3H, CHCH_3, $^3J_{H\text{-}H}$ = 6.9 Hz), 1.40 (s, 9H, C(CH$_3$)$_3$), 1.95 (m, 1H, CHCH$_3$), 1.95 (s, 3H, CH$_3$), 3.04 (brd, 2H, NCH$_2$, $^3J_{H\text{-}H}$ = 6.5 Hz), 3.92 (dd, 1H, H_A-OCH$_2$, $^2J_{A\text{-}B}$ = 11.2 Hz, $^3J_{H\text{-}A}$ = 6.2 Hz), 3.98 (dd, 1H, H_B-OCH$_2$, $^2J_{A\text{-}B}$ = 11.2 Hz, $^3J_{H\text{-}B}$ = 5.4 Hz), 4.75 (brs, 1H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 14.3 (CH$_3$), 20.8 (CH$_3$), 28.3 (C(CH$_3$)$_3$), 33.4 (CHCH$_3$), 43.3 (NCH$_2$), 66.7 (OCH$_2$), 79.2 (C(CH$_3$)$_3$), 156.0 (C=O), 171.2 (C=O).

Separation of enantiomers by GC on Lipodex E (25 m×0.25 mm).

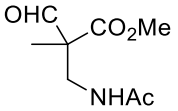
5.1.2.4 Synthesis of functionalized β^2-homoalanine derivatives

General procedure for the asymmetric hydroformylation of methyl (2-acetamidomethyl)acrylate (**6a**)

The substrate (1.0 eq), Rh(acac)(CO)$_2$ (1 mol%) and the ligand (1.2 mol%) are transferred into a vial, which is placed into a stainless steel autoclave. The solvent (8 mL/1.0 mmol substrate) is added under an argon atmosphere and the autoclave is purged with argon (three times) followed by syngas (three times). The indicated reaction conditions (syngas pressure, temperature and reaction time) are adjusted by an automatic program. After stirring for the adjusted time, the mixture is cooled to room temperature, depressurized and concentrated *in vacuo*. The reaction mixture is analyzed by ^{1}H NMR.

The enantiomeric excess is determined by GC analysis. A racemic mixture of **14**, as sample for the quantitative and qualitative analysis, is prepared by the hydroformylation of **6a** with 1 mol% $Rh(acac)(CO)_2$ and 6 mol% $P(OPh)_3$ in toluene.

Methyl 3-acetamido-2-formyl-2-methylpropanoate (**14**)



^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.32 (s, 3H, CCH_3), 2.08 (s, 2H, CH_2), 1.91 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 6.29 (brs, 1H, NH), 9.56 (s, 1H, CHO).

^{13}C NMR spectrum could not be analyzed due to the small amount in the final reaction mixture.

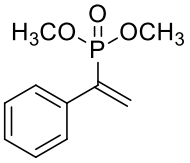
Separation of enantiomers by GC on Lipodex E (25 m×0.25 mm), 100/30-8-180/10; t_R = 31.4 min for (+)-enantiomer and t_R = 31.6 min for (–)-enantiomer.

5.1.2.5 Synthesis of 3-aryl-3-phosphorylated propanals

General procedure for the synthesis of 1-aryl-1-phosphorylated ethenes **16a-g**

The corresponding acetophenone or 2-acetonaphthone (1.0 eq) is placed in 3-necked flask and it is cooled to 0 °C. Phosphorus trichloride (1.4 eq) is added via dropping funnel and the mixture is stirred at room temperature for 1 h. Then, it is cooled to 0 °C again and acetic acid (2.5 eq) is added via dropping funnel. The solution is stirred at room temperature for 16 h. After that time, ice is added so that a white solid precipitates. The mixture is stirred at room temperature for 16 h. Water is then distillied off (oil bath, 160 °C), hot aqueous HCl (0.4 mL/1.0 mmol substrate) is added in one portion and the solution is refluxed for 2 h. After cooling to room temperature, the corresponding phosphonic acid precipitates, what is filtered off and dried *in vacuo*. The solid is used in a further step without purification.
1.0 Eq of the corresponding phosphonic acid is mixed with trimethyl orthoformate and triethyl orthoformate (4.5 eq), respectively, and the solution is stirred at 100 °C for 30 min. Then, formed methyl formate and methanol (or ethyl formate and ethanol) are distilled off and the solution is refluxed for further 90 min. The mixture is cooled to room temperature, concentrated *in vacuo* and purified by column chromatography to give **16a-g**.

Dimethyl (1-phenylvinyl)phosphonate (**16a**)[146]



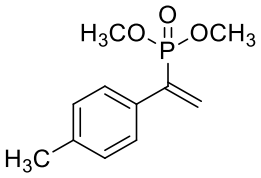
Starting from acetophenone (12.2 g, 100 mmol), PCl_3 (19.2 g, 140 mmol) and HOAc (15.0 g, 250 mmol), (1-phenylvinyl)phosphonic acid could be obtained as an off-white solid (16.0 g, 87 %). Starting from the phosphonic acid (5.0 g, 27.2 mmol) and trimethyl orthoformate (13.00 g, 122.2 mmol), the product **16a** was isolated as a yellowish liquid (4.00 g, 69 %) after column chromatography (EtOAc).

^{31}P{^{1}H} NMR (121 MHz, $CDCl_3$): δ (ppm) = 19.8 (s).

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.70 (d, 6H, $2OCH_3$, $^3J_{H\text{-}P}$ = 11.1 Hz), 6.15 (dd, 1H, H_A-CH_2, $J_{A\text{-}P}$ = 46.2 Hz, $J_{A\text{-}B}$ = 1.4 Hz), 6.30 (dd, 1H, H_B-CH_2, $J_{B\text{-}P}$ = 22.2 Hz, $J_{A\text{-}B}$ = 1.4 Hz), 7.27-7.35 (m, 3H, CH-Ar), 7.45-7.49 (m, 2H, CH-Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 52.6 (d, $2OCH_3$, $J_{C\text{-}P}$ = 5.8 Hz), 127.3 (d, $2CH_{Ar}$, $J_{C\text{-}P}$ = 5.8 Hz), 128.3 (d, CH_{Ar}, $J_{C\text{-}P}$ = 0.9 Hz), 128.4 ($2CH_{Ar}$), 132.3 (d, CH_2, $J_{C\text{-}P}$ = 8.1 Hz), 136.4 (d, C_{Ar}, $J_{C\text{-}P}$ = 11.8 Hz), 138.5 (d, CCH_2, $J_{C\text{-}P}$ = 175.2 Hz).

Dimethyl (1-(*p*-tolyl)vinyl)phosphonate (**16b**)



Starting from 1-(*p*-tolyl)ethanone (13.4 g, 100 mmol), PCl_3 (19.2 g, 140 mmol) and HOAc (15.0 g, 250 mmol), (1-(*p*-tolyl)vinyl)phosphonic acid could be obtained as an off-white solid (19.8 g, 99 %). Starting from the phosphonic acid (4.96 g, 25.0 mmol) and trimethyl orthoformate (11.94 g, 112.5 mmol), the product **16b** was isolated as a yellowish liquid (2.30 g, 41 %) after column chromatography (EtOAc).

Anal. calcd for $C_{11}H_{15}O_3P$: C, 58.41; H, 6.68. Found: C, 58.15; H, 6.43 %.

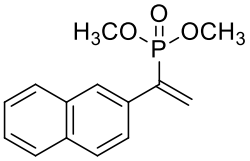
HRMS (EI) calculated for $C_{11}H_{15}O_3P$ 226.07533, found 226.07498.

$^{31}P\{^1H\}$ NMR (121 MHz, $CDCl_3$): δ (ppm) = 20.2 (s).

^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.31 (s, 3H, CH_3), 3.69 (d, 6H, $2OCH_3$, $^3J_{H\text{-}P}$ = 11.1 Hz), 6.12 (dd, 1H, H_A-CH_2, $J_{A\text{-}P}$ = 46.4 Hz, $J_{A\text{-}B}$ = 1.4 Hz), 6.26 (dd, 1H, H_B-CH_2, $J_{B\text{-}P}$ = 22.1 Hz, $J_{A\text{-}B}$ = 1.4 Hz), 7.12 (d, 2H, CH-Ar, $^3J_{H\text{-}H}$ = 7.8 Hz), 7.35-7.39 (m, 2H, CH-Ar).

^{13}C NMR (63 MHz, $CDCl_3$): δ (ppm) = 20.9 (CH_3), 52.4 (d, $2OCH_3$, $J_{C\text{-}P}$ = 5.8 Hz), 127.0 (d, $2CH_{Ar}$, $J_{C\text{-}P}$ = 5.9 Hz), 129.0 ($2CH_{Ar}$), 131.4 (d, CH_2, $J_{C\text{-}P}$ = 8.1 Hz), 133.3 (d, C_{Ar}, $J_{C\text{-}P}$ = 11.7 Hz), 138.1 (d, *C*CH_2, $J_{C\text{-}P}$ = 174.3 Hz), 138.1 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.2 Hz).

Dimethyl (1-(naphthalen-2-yl)vinyl)phosphonate (**16c**)



Starting from 1-(naphthalen-2-yl)ethanone (8.5 g, 50 mmol), PCl_3 (9.6 g, 70 mmol) and HOAc (7.5 g, 125 mmol), (1-(naphthalen-2-yl)vinyl)phosphonic acid could be obtained as an off-white solid (11.1 g, 96 %). Starting from the phosphonic acid (5.86 g, 25.0 mmol) and trimethyl orthoformate (11.94 g, 112.5 mmol), the product **16c** was isolated as a yellowish liquid (3.80 g, 60 %) after column chromatography (EtOAc).

Anal. calcd for $C_{14}H_{15}O_3P$: C, 64.12; H, 5.77. Found: C, 64.64; H, 6.13 %.

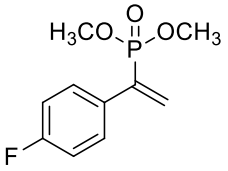
HRMS (EI) calculated for $C_{14}H_{15}O_3P$ 262.07533, found 262.07504.

$^{31}P\{^1H\}$ NMR (121 MHz, $CDCl_3$): δ (ppm) = 19.9 (s).

^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.59 (d, 6H, $2OCH_3$, $^3J_{H\text{-}P}$ = 11.1 Hz), 6.12 (dd, 1H, H_A-CH_2, $J_{A\text{-}P}$ = 45.9 Hz, $J_{A\text{-}B}$ = 1.2 Hz), 6.26 (dd, 1H, H_B-CH_2, $J_{B\text{-}P}$ = 22.0 Hz, $J_{A\text{-}B}$ = 1.2 Hz), 7.27-7.30 (m, 2H, CH-Ar), 7.44-7.47 (m, 1H, CH-Ar), 7.62-7.71 (m, 3H, CH-Ar), 7.87 (brs, 1H, CH-Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 52.3 (d, $2OCH_3$, $J_{C\text{-}P}$ = 5.5 Hz), 124.6 (d, CH_{Ar}, $J_{C\text{-}P}$ = 6.1 Hz), 126.0 (CH_{Ar}), 126.1 (CH_{Ar}), 126.4 (d, CH_{Ar}, $J_{C\text{-}P}$ = 6.1 Hz), 127.2 (CH_{Ar}), 127.8 (CH_{Ar}), 128.0 (CH_{Ar}), 132.7 (d, CH_2, $J_{C\text{-}P}$ = 7.7 Hz), 132.7 (C_{Ar}), 132.8 (C_{Ar}), 133.4 (d, C_{Ar}, $J_{C\text{-}P}$ = 12.1 Hz), 138.2 (d, *C*CH_2, $J_{C\text{-}P}$ = 175.0 Hz).

Dimethyl (1-(4-fluorophenyl)vinyl)phosphonate (**16d**)



Starting from 1-(4-fluorophenyl)ethanone (6.9 g, 50 mmol), PCl_3 (9.6 g, 70 mmol) and HOAc (7.5 g, 125 mmol), (1-(4-fluorophenyl)vinyl)phosphonic acid could be obtained as a white solid (8.8 g, 87 %). Starting from the phosphonic acid (5.06 g, 25.0 mmol) and trimethyl orthoformate (11.94 g, 112.5 mmol), the product **16d** was isolated as a yellowish liquid (4.00 g, 70 %)

after column chromatography (EtOAc).

Anal. calcd for $C_{10}H_{12}FO_3P$: C, 52.18; H, 5.25. Found: C, 52.22; H, 5.29 %.

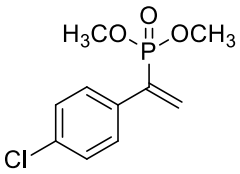
HRMS (EI) calculated for $C_{10}H_{12}FO_3P$ 230.05026, found 230.05011.

$^{31}P\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ (ppm) = 19.4 (s).

^1H NMR (250 MHz, $CDCl_3$): δ (ppm) = 3.67 (d, 6H, $2OCH_3$, $^3J_{H\text{-}P}$ = 11.1 Hz), 6.07 (dd, 1H, H_A-CH_2, $J_{A\text{-}P}$ = 45.8 Hz, $J_{A\text{-}B}$ = 1.2 Hz), 6.24 (dd, 1H, H_B-CH_2, $J_{B\text{-}P}$ = 22.0 Hz, $J_{A\text{-}B}$ = 1.2 Hz), 6.93-7.00 (m, 2H, CH-Ar), 7.39-7.45 (m, 2H, CH-Ar).

^{13}C NMR (63 MHz, $CDCl_3$): δ (ppm) = 52.5 (d, $2OCH_3$, $J_{C\text{-}P}$ = 5.8 Hz), 115.3 (d, $2CH_{Ar}$, J = 21.7 Hz), 129.0 (m, $2CH_{Ar}$), 131.9 (dd, CH_2, $J_{C\text{-}P}$ = 7.9 Hz, $J_{C\text{-}F}$ = 1.1 Hz), 132.3 (dd, C_{Ar}, $J_{C\text{-}P}$ = 12.1 Hz, $J_{C\text{-}F}$ = 3.5 Hz), 137.4 (d, *C*CH_2, $J_{C\text{-}P}$ = 176.3 Hz), 162.8 (dd, C_{Ar}, $J_{C\text{-}F}$ = 248.1 Hz, $J_{C\text{-}P}$ = 1.3 Hz).

Dimethyl (1-(4-chlorophenyl)vinyl)phosphonate (**16e**)



Starting from 1-(4-chlorophenyl)ethanone (15.5 g, 100 mmol), PCl_3 (19.2 g, 140 mmol) and HOAc (15.0 g, 250 mmol), (1-(4-chlorophenyl)vinyl)phosphonic acid could be obtained as a white solid (20.8 g, 95 %). Starting from the phosphonic acid (5.47 g, 25.0 mmol) and trimethyl orthoformate (11.94 g, 112.5 mmol), the product **16e** was isolated as a yellowish liquid (5.20 g, 84 %) after column chromatography (EtOAc).

Anal. calcd for $C_{10}H_{12}ClO_3P$: C, 48.70; H, 4.90. Found: C, 48.64; H, 4.83 %.

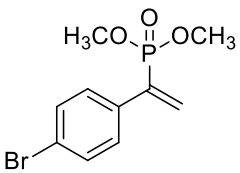
HRMS (EI) calculated for $C_{10}H_{12}ClO_3P$ 246.02071, found 246.02024.

$^{31}P\{^1H\}$ NMR (121 MHz, $CDCl_3$): δ (ppm) = 19.2 (s).

^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.68 (d, 6H, $2OCH_3$, $^3J_{H\text{-}P}$ = 11.1 Hz), 6.10 (dd, 1H, H_A-CH_2, $J_{A\text{-}P}$ = 45.7 Hz, $J_{A\text{-}B}$ = 1.3 Hz), 6.26 (dd, 1H, H_B-CH_2, $J_{B\text{-}P}$ = 22.0 Hz, $J_{A\text{-}B}$ = 1.2 Hz), 7.24-7.28 (m, 2H, CH-Ar), 7.37-7.40 (m, 2H, CH-Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 52.5 (d, $2OCH_3$, $J_{C\text{-}P}$ = 5.8 Hz), 128.5 ($2CH_{Ar}$), 128.5 (d, $2CH_{Ar}$), 132.3 (d, CH_2, $J_{C\text{-}P}$ = 7.6 Hz), 134.2 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.2 Hz), 134.7 (d, C_{Ar}, $J_{C\text{-}P}$ = 12.1 Hz), 137.4 (d, *C*CH_2, $J_{C\text{-}P}$ = 176.6 Hz).

Dimethyl (1-(4-bromophenyl)vinyl)phosphonate (**16f**)



Starting from 1-(4-bromophenyl)ethanone (19.9 g, 100 mmol), PCl_3 (19.2 g, 140 mmol) and HOAc (15.0 g, 250 mmol), (1-(4-bromophenyl)vinyl)phosphonic acid could be obtained as a white solid (26.1 g, 99 %). Starting from the phosphonic acid (6.58 g, 25.0 mmol) and trimethyl orthoformate (11.94 g, 112.5 mmol), the product **16f** was isolated as a yellowish liquid (4.50 g, 62 %) after column chromatography (EtOAc).

Anal. calcd for $C_{10}H_{12}BrO_3P$: C, 41.26; H, 4.16. Found: C, 41.57; H, 4.14 %.

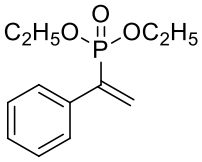
HRMS (EI) calculated for $C_{10}H_{12}BrO_3P$ 289.97019, found 289.96088.

$^{31}P\{^1H\}$ NMR (121 MHz, $CDCl_3$): δ (ppm) = 19.1 (s).

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.70 (d, 6H, $2OCH_3$, $^{3}J_{H\text{-}P}$ = 11.1 Hz), 6.13 (dd, 1H, H_A-CH_2, $J_{A\text{-}P}$ = 45.8 Hz, $J_{A\text{-}B}$ = 1.0 Hz), 6.30 (dd, 1H, H_B-CH_2, $J_{B\text{-}P}$ = 22.0 Hz, $J_{A\text{-}B}$ = 1.0 Hz), 7.32-7.35 (m, 2H, CH-Ar), 7.42-7.45 (m, 2H, CH-Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 52.6 (d, $2OCH_3$, $J_{C\text{-}P}$ = 6.1 Hz), 122.6 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.6 Hz), 128.9 (d, $2CH_{Ar}$, $J_{C\text{-}P}$ = 6.1 Hz), 131.5 ($2CH_{Ar}$), 132.5 (d, CH_2, $J_{C\text{-}P}$ = 7.7 Hz), 135.2 (d, C_{Ar}, $J_{C\text{-}P}$ = 12.1 Hz), 137.7 (d, *C*CH_2, $J_{C\text{-}P}$ = 177.2 Hz).

Diethyl (1-phenylvinyl)phosphonate (**16g**)[146]



Starting from the phosphonic acid (4.60 g, 25.0 mmol) and triethyl orthoformate (16.67 g, 112.5 mmol), the product **16g** was isolated as a yellowish liquid (4.02 g, 67 %) after column chromatography (EtOAc).

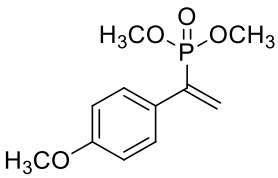
^{31}P{^{1}H} NMR (121 MHz, $CDCl_3$): δ (ppm) = 17.0 (s).

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.27 (t, 6H, $2CH_3$, $^{3}J_{H\text{-}H}$ = 7.1 Hz), 4.00-4.19 (m, 4H, $2OCH_2$), 6.14 (dd, 1H, H_A-CH_2, $J_{A\text{-}P}$ = 45.8 Hz, $J_{A\text{-}B}$ = 1.5 Hz), 6.33 (dd, 1H, H_B-CH_2, $J_{B\text{-}P}$ = 22.0 Hz, $J_{A\text{-}B}$ = 1.5 Hz), 7.24-7.28 (m, 2H, CH-Ar), 7.30-7.37 (m, 3H, CH-Ar), 7.50-7.54 (m, 2H, CH-Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 16.2 (d, $2CH_3$, $J_{C\text{-}P}$ = 6.6 Hz), 62.2 (d, $2OCH_2$, $J_{C\text{-}P}$ = 5.5 Hz), 127.4 (d, $2CH_{Ar}$, $J_{C\text{-}P}$ = 5.5 Hz), 128.2 (CH_{Ar}), 128.4 ($2CH_{Ar}$), 131.7 (d, CH_2, $J_{C\text{-}P}$ = 8.3 Hz), 138.6 (d, *C*CH_2, $J_{C\text{-}P}$ = 174.4 Hz), 159.7 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.1 Hz).

Procedure for the synthesis of dimethyl (1-(4-methoxyphenyl)vinyl)phosphonate (**16h**)

trans-4-Methoxy-β-nitrostyrene (3.58 g 20.0 mmol) is dissolved in dimethyl ether (20 mL) and trimethyl phosphite (2.73 g, 22.0 mmol) is added slowly via syringe. The mixture is stirred at room temperature for 9 d. Then, it is concentrated *in vacuo* and the resulting oil is purified by column chromatography (heptane/EtOAc = 3:1) to yield **16h** as a yellowish liquid (3.32 g, 69 %).



Anal. calcd for $C_{11}H_{15}O_4P$: C, 54.55; H, 6.24. Found: C, 54.21; H, 5.95 %.

HRMS (EI) calculated for $C_{11}H_{15}O_4P$ 242.07025, found 242.07003.

^{31}P{^{1}H} NMR (121 MHz, $CDCl_3$): δ (ppm) = 20.4 (s).

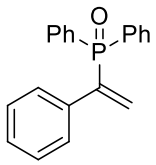
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.72 (d, 6H, $2OCH_3$, $^{3}J_{H\text{-}P}$ = 11.1 Hz), 3.80 (s, 3H, $PhOCH_3$), 6.11 (dd, 1H, H_A-CH_2, $J_{A\text{-}P}$ = 46.4 Hz, $J_{A\text{-}B}$ = 1.4 Hz), 6.24 (dd, 1H, H_B-CH_2, $J_{B\text{-}P}$ = 22.1 Hz, $J_{A\text{-}B}$ = 1.4 Hz), 6.85-6.88 (m, 2H, CH-Ar), 7.42-7.47 (m, 2H, CH-Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 52.6 (d, $2OCH_3$, $J_{C\text{-}P}$ = 6.1 Hz), 55.2 ($PhOCH_3$), 113.9 ($2CH_{Ar}$), 128.5 (d, $2CH_{Ar}$, $J_{C\text{-}P}$ = 6.1 Hz), 130.7 (d, CH_2, $J_{C\text{-}P}$ = 8.8 Hz), 136.7 (d, C_{Ar}, $J_{C\text{-}P}$ = 11.6 Hz), 139.8 (d, *C*CH_2, $J_{C\text{-}P}$ = 174.4 Hz).

Procedure for the synthesis of diphenyl(1-phenylvinyl)phosphine oxide (**16i**)[147]

Phenylacetylene (536 mg, 5.3 mmol), diphenylphosphine oxide (1.01 g, 5.0 mmol), palladium(II) acetate (56 mg, 0.25 mmol) and dppe (139 mg, 0.35 mmol) are dissolved in toluene (20 mL) and the mixture is stirred at 100 °C for 14 h. After cooling to room temperature, it is concentrated *in vacuo* to

yield product **16i** as a yellowish liquid (0.88 g, 73 %) after column chromatography (heptane/EtOAc = 1:1).



$^{31}P\{^{1}H\}$ NMR (121 MHz, $CDCl_3$): δ (ppm) = 30.0 (s).

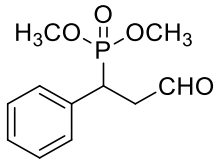
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.76 (dd, 1H, H_A-CH_2, J_{A-P} = 19.7 Hz, J_{A-B} = 1.1 Hz), 6.26 (dd, 1H, H_B-CH_2, J_{B-P} = 40.2 Hz, J_{A-B} = 1.0 Hz), 7.22-7.28 (m, 3H, CH-Ar), 7.41-7.55 (m, 8H, CH-Ar), 7.69-7.77 (m, 4H, CH-Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 128.2 (d, J_{C-P} = 5.0 Hz), 128.2, 128.3, 128.4, 128.5, 131.7 (d, $2C_{Ar}$, J_{C-P} = 104.1 Hz), 131.9 (d, CH_2, J_{C-P} = 9.2 Hz), 132.0, 132.1, 144.4 (d, C, J_{C-P} = 93.6 Hz).

General procedure for the asymmetric hydroformylation of 1-aryl-1-phosphorylated ethenes **16a-i**

The substrate (1.0 eq), $Rh(acac)(CO)_2$ (1 mol%) and the ligand (1.2 mol%) are transferred into a vial, which is placed into a stainless steel autoclave. The solvent (8 mL/1.0 mmol substrate) is added under an argon atmosphere and the autoclave is purged with argon (three times) followed by syngas (three times). The indicated reaction conditions (syngas pressure, temperature and reaction time) are adjusted by an automatic program. After stirring for the adjusted time, the mixture is cooled to room temperature, depressurized and concentrated *in vacuo*. The reaction mixture is analyzed by ^{31}P- and ^{1}H NMR. The enantiomeric excess is determined by GC analysis. Racemic mixtures of **17a-i**, as samples for the quantitative and qualitative analysis, are prepared by the hydroformylation of **16a-i** with 1 mol% $Rh(acac)(CO)_2$ and 5 mol% Alkanox® 240 in toluene.

Dimethyl (3-oxo-1-phenylpropyl)phosphonate (**17a**)



Anal. calcd for $C_{11}H_{15}O_4P$: C, 54.55; H, 6.24. Found: C, 54.68; H, 6.33 %.

HRMS (EI) calculated for $C_{11}H_{15}O_4P$ 242.07025, found 242.07001.

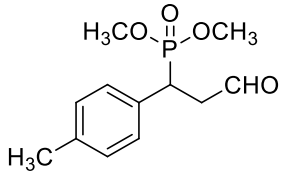
$^{31}P\{^{1}H\}$ NMR (121 MHz, $CDCl_3$): δ (ppm) = 29.6 (s).

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.03 (m, 2H, CH_2), 3.49 (d, 3H, OCH_3, $^{3}J_{H-P}$ = 10.6 Hz), 3.68 (d, 3H, OCH_3, $^{3}J_{H-P}$ = 10.8 Hz), 3.70-3.84 (m, 1H, CH), 7.22-7.38 (m, 5H, CH-Ar), 9.65 (m, 1H, CHO).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 37.1 (d, CH, J_{C-P} = 141.2 Hz), 43.7 (d, CH_2, J_{C-P} = 2.4 Hz), 52.7 (d, OCH_3, J_{C-P} = 7.4 Hz), 53.5 (d, OCH_3, J_{C-P} = 7.1 Hz), 127.5 (d, CH_{Ar}, J_{C-P} = 3.2 Hz), 128.6 (d, $2CH_{Ar}$, J_{C-P} = 2.6 Hz), 128.9 (d, $2CH_{Ar}$, J_{C-P} = 6.5 Hz), 134.8 (d, C_{Ar}, J_{C-P} = 7.2 Hz), 198.4 (d, CHO, J_{C-P} = 15.1 Hz).

Separation of enantiomers by GC on Lipodex E (25 m×0.25 mm), 80/30-8-200/10; t_R = 55.2 min for (+)-enantiomer and t_R = 55.6 min for (–)-enantiomer.

Dimethyl (3-oxo-1-(*p*-tolyl)propyl)phosphonate (**17b**)



Anal. calcd for $C_{12}H_{17}O_4P$: C, 56.25; H, 6.69. Found: C, 56.64; H, 6.88 %.

HRMS (EI) calculated for $C_{12}H_{17}O_4P$ 256.08590, found 256.08545.

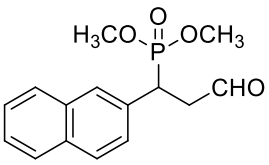
$^{31}P\{^{1}H\}$ NMR (121 MHz, $CDCl_3$): δ (ppm) = 29.8 (s).

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.30 (d, 3H, CH_3, $^{3}J_{H-H}$ = 2.0 Hz),

3.03-3.14 (m, 2H, CH_2), 3.49 (d, 3H, OCH_3, $^3J_{H-P}$ = 10.5 Hz), 3.66 (d, 3H, OCH_3, $^3J_{H-P}$ = 10.7 Hz), 3.68-3.78 (m, 1H, CH), 7.08-7.13 (m, 2H, CH-Ar), 7.20-7.24 (m, 2H, CH-Ar), 9.63 (m, 1H, CHO).

^{13}C NMR (63 MHz, $CDCl_3$): δ (ppm) = 21.0 (CH_3), 36.9 (d, CH, J_{C-P} = 141.6 Hz), 43.8 (d, CH_2, J_{C-P} = 2.0 Hz), 52.9 (d, OCH_3, J_{C-P} = 7.3 Hz), 53.7 (d, OCH_3, J_{C-P} = 7.1 Hz), 128.8 (d, $2CH_{Ar}$, J_{C-P} = 6.6 Hz), 129.5 (d, $2CH_{Ar}$, J_{C-P} = 2.7 Hz), 131.6 (d, C_{Ar}, J_{C-P} = 7.3 Hz), 137.4 (d, C_{Ar}, J_{C-P} = 3.2 Hz), 198.7 (d, CHO, J_{C-P} = 15.5 Hz).

Dimethyl (1-(naphthalene-2-yl)-3-oxopropyl)phosphonate (**17c**)



Anal. calcd for $C_{15}H_{17}O_4P$: C, 61.64; H, 5.86. Found: C, 61.30; H, 5.81 %.

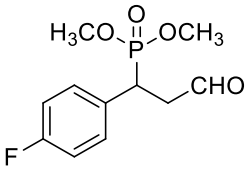
HRMS (EI) calculated for $C_{15}H_{17}O_4P$ 292.08590, found 292.08573.

$^{31}P\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ (ppm) = 29.4 (s).

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.20-3.27 (m, 2H, CH_2), 3.48 (d, 3H, OCH_3, $^3J_{H-P}$ = 10.4 Hz), 3.69 (d, 3H, OCH_3, $^3J_{H-P}$ = 10.7 Hz), 3.87-4.00 (m, 1H, CH), 7.41-7.51 (m, 3H, CH-Ar), 7.76-7.82 (m, 4H, CH-Ar), 9.67 (m, 1H, CHO).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 37.3 (d, CH, J_{C-P} = 141.2 Hz), 43.9 (d, CH_2, J_{C-P} = 2.3 Hz), 52.8 (d, CH_3, J_{C-P} = 7.2 Hz), 53.6 (d, CH_3, J_{C-P} = 7.1 Hz), 126.1 (d, CH_{Ar}, J_{C-P} = 1.3 Hz), 126.2 (d, CH_{Ar}, J_{C-P} = 0.9 Hz), 126.7 (d, CH_{Ar}, J_{C-P} = 5.3 Hz), 127.5 (d, CH_{Ar}, J_{C-P} = 1.2 Hz), 127.7 (d, CH_{Ar}, J_{C-P} = 1.1 Hz), 127.9 (d, CH_{Ar}, J_{C-P} = 8.3 Hz), 128.4 (d, CH_{Ar}, J_{C-P} = 2.1 Hz), 132.3 (d, C_{Ar}, J_{C-P} = 7.3 Hz), 132.6 (d, C_{Ar}, J_{C-P} = 2.3 Hz), 133.2 (d, C_{Ar}, J_{C-P} = 2.6 Hz), 198.4 (d, CHO, J_{C-P} = 15.2 Hz).

Dimethyl (1-(4-fluorophenyl)-3-oxopropyl)phosphonate (**17d**)



Anal. calcd for $C_{11}H_{14}FO_4P$: C, 50.78; H, 5.42. Found: C, 50.55; H, 5.11 %.

HRMS (EI) calculated for $C_{11}H_{14}FO_4P$ 260.06083, found 260.06042.

^{19}F NMR (282 MHz, $CDCl_3$): δ (ppm) = -114.6 (d, J = 5.1 Hz).

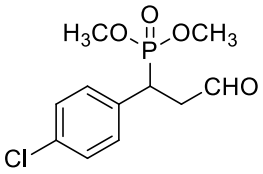
$^{31}P\{^1H\}$ NMR (121 MHz, $CDCl_3$): δ (ppm) = 29.4 (s).

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.04-3.25 (m, 2H, CH_2), 3.54 (d, 3H, OCH_3, $^3J_{H-P}$ = 10.6 Hz), 3.71 (d, 3H, OCH_3, $^3J_{H-P}$ = 10.8 Hz), 3.74-3.84 (m, 1H, CH), 6.99-7.07 (m, 2H, CH-Ar), 7.31-7.38 (m, 2H, CH-Ar), 9.67 (m, 1H, CHO).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 36.3 (d, CH, J_{C-P} = 142.1 Hz), 43.9 (d, CH_2, J_{C-P} = 1.8 Hz), 52.9 (d, CH_3, J_{C-P} = 7.3 Hz), 53.6 (d, CH_3, J_{C-P} = 7.0 Hz), 115.6 (d, $2CH_{Ar}$, J_{C-P} = 21.5 Hz, J_{C-F} = 2.6 Hz), 130.4-130.6 (m, $2CH_{Ar}$), 162.1 (dd, C_{Ar}, J_{C-F} = 246.8 Hz, J_{C-P} = 3.5 Hz), 172.1 (d, C_{Ar}, J_{C-P} = 19.5 Hz), 198.2 (d, CHO, J_{C-P} = 15.4 Hz).

Separation of enantiomers by GC on Lipodex E (25 m×0.25 mm), 140/40-6-180/30; t_R = 48.2 min for (+)-enantiomer and t_R = 48.7 min for (–)-enantiomer.

Dimethyl (1-(4-chlorophenyl)-3-oxopropyl)phosphonate (**17e**)



Anal. calcd for $C_{11}H_{14}ClO_4P$: C, 47.76; H, 5.10. Found: C, 47.87; H, 5.25 %.

HRMS (EI) calculated for $C_{11}H_{14}ClO_4P$ 276.03127, found 276.03208.

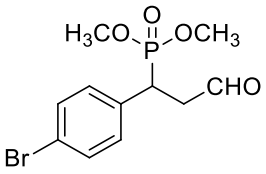
$^{31}P\{^1H\}$ NMR (121 MHz, $CDCl_3$): δ (ppm) = 29.1 (s).

^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.03-3.24 (m, 2H, CH_2), 3.54 (d, 3H, OCH_3, $^3J_{H\text{-}P}$ = 10.7 Hz), 3.70 (d, 3H, OCH_3, $^3J_{H\text{-}P}$ = 10.7 Hz), 3.72-3.81 (m, 1H, CH), 7.30 (m, 4H, CH-Ar), 9.67 (m, 1H, CHO).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 36.6 (d, CH, $J_{C\text{-}P}$ = 141.9 Hz), 43.9 (d, CH_2, $J_{C\text{-}P}$ = 2.2 Hz), 53.0 (d, CH_3, $J_{C\text{-}P}$ = 7.4 Hz), 53.8 (d, CH_3, $J_{C\text{-}P}$ = 6.8 Hz), 129.0 (d, $2CH_{Ar}$, $J_{C\text{-}P}$ = 2.5 Hz), 130.3 (d, $2CH_{Ar}$, $J_{C\text{-}P}$ = 6.6 Hz), 133.6 (d, C_{Ar}, $J_{C\text{-}P}$ = 7.5 Hz), 133.6 (m, C_{Ar}), 198.1 (d, CHO, $J_{C\text{-}P}$ = 15.3 Hz).

Separation of enantiomers by GC on Lipodex E (25 m×0.25 mm), 140/40-6-180/30; t_R = 48.5 min for (+)-enantiomer and t_R = 49.0 min for (–)-enantiomer.

Dimethyl (1-(4-bromophenyl)-3-oxopropyl)phosphonate (**17f**)



Anal. calcd for $C_{11}H_{14}BrO_4P$: C, 41.14; H, 4.39. Found: C, 41.53; H, 4.77 %.

HRMS (EI) calculated for $C_{11}H_{14}BrO_4P$ 319.98076, found 319.98051.

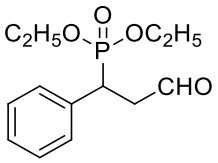
$^{31}P\{1H\}$ NMR (101 MHz, $CDCl_3$): δ (ppm) = 29.9 (s).

^1H NMR (250 MHz, $CDCl_3$): δ (ppm) = 3.01-3.24 (m, 2H, CH_2), 3.51 (d, 3H, OCH_3, $^3J_{H\text{-}P}$ = 10.6 Hz), 3.67 (d, 3H, OCH_3, $^3J_{H\text{-}P}$ = 10.7 Hz), 3.71-3.83 (m, 1H, CH), 7.18-7.25 (m, 2H, CH-Ar), 7.40-7.45 (m, 2H, CH-Ar), 9.63 (m, 1H, CHO).

^{13}C NMR (63 MHz, $CDCl_3$): δ (ppm) = 36.6 (d, CH, $J_{C\text{-}P}$ = 142.1 Hz), 43.7 (d, CH_2, $J_{C\text{-}P}$ = 2.2 Hz), 53.0 (d, OCH_3, $J_{C\text{-}P}$ = 7.4 Hz), 53.7 (d, OCH_3, $J_{C\text{-}P}$ = 7.1 Hz), 121.6 (d, C_{Ar}, $J_{C\text{-}P}$ = 4.0 Hz), 130.6 (d, $2CH_{Ar}$, $J_{C\text{-}P}$ = 6.6 Hz), 131.8 (d, $2CH_{Ar}$, $J_{C\text{-}P}$ = 2.6 Hz), 134.0 (d, C_{Ar}, $J_{C\text{-}P}$ = 7.3 Hz), 198.0 (d, CHO, $J_{C\text{-}P}$ = 15.2 Hz).

Separation of enantiomers by GC on Lipodex E (25 m×0.25 mm), 140/40-6-180/30; t_R = 48.6 min for (+)-enantiomer and t_R = 49.3 min for (–)-enantiomer.

Diethyl (3-oxo-1-phenylpropyl)phosphonate (**17g**)



Anal. calcd for $C_{13}H_{19}O_4P$: C, 57.77; H, 7.09. Found: C, 57.51; H, 6.82 %.

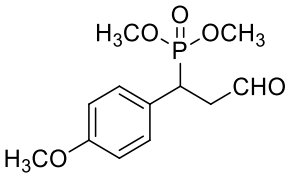
HRMS (EI) calculated for $C_{13}H_{19}O_4P$ 270.10155, found 270.10122.

$^{31}P\{^1H\}$ NMR (121 MHz, $CDCl_3$): δ (ppm) = 27.2 (s).

^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.12 (t, 3H, OCH_3, $^3J_{H\text{-}H}$ = 7.1 Hz), 1.29 (t, 3H, OCH_3, $^3J_{H\text{-}H}$ = 7.1 Hz), 3.06-3.26 (m, 2H, CH_2), 3.69-4.17 (m, 5H, CH and $2OCH_2$), 7.23-7.40 (m, 5H, CH-Ar), 9.68 (m, 1H, CHO).

^{13}C NMR (63 MHz, $CDCl_3$): δ (ppm) = 16.0 (d, CH_3, $J_{C\text{-}P}$ = 5.8 Hz), 16.3 (d, CH_3, $J_{C\text{-}P}$ = 5.9 Hz), 37.7 (d, CH, $J_{C\text{-}P}$ = 141.4 Hz), 43.8 (d, CH_2, $J_{C\text{-}P}$ = 2.3 Hz), 62.1 (d, OCH_2, $J_{C\text{-}P}$ = 7.4 Hz), 62.8 (d, OCH_2, $J_{C\text{-}P}$ = 7.1 Hz), 127.4 (d, CH_{Ar}, $J_{C\text{-}P}$ = 3.4 Hz), 128.5 (d, $2CH_{Ar}$, $J_{C\text{-}P}$ = 2.6 Hz), 129.0 (d, $2CH_{Ar}$, $J_{C\text{-}P}$ = 6.5 Hz), 135.0 (d, C_{Ar}, $J_{C\text{-}P}$ = 7.1 Hz), 198.8 (d, CHO, $J_{C\text{-}P}$ = 15.3 Hz).

Dimethyl (1-(4-methoxyphenyl)-3-oxopropyl)phosphonate (**17h**)



Anal. calcd for $C_{12}H_{17}O_5P$: C, 52.94; H, 6.29. Found: C, 52.64; H, 6.08 %.

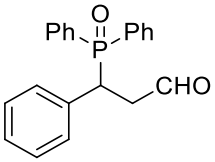
HRMS (EI) calculated for $C_{12}H_{17}O_5P$ 272.08081, found 272.08058.

$^{31}P\{1H\}$ NMR (101 MHz, $CDCl_3$): δ (ppm) = 29.8 (s).

^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) = 3.00-3.21 (m, 2H, CH_2), 3.49 (d, 3H, OCH_3, $^{3}J_{H\text{-}P}$ = 10.6 Hz), 3.67 (d, 3H, OCH_3, $^{3}J_{H\text{-}P}$ = 10.7 Hz), 3.77 (s, 3H, $PhOCH_3$), 3.73 (m, 1H, CH), 6.85 (m, 2H, CH-Ar), 7.24-7.28 (m, 2H, CH-Ar), 9.64 (m, 1H, CHO).

^{13}C NMR (63 MHz, $CDCl_3$): δ (ppm) = 36.5 (d, CH, $J_{C\text{-}P}$ = 142.3 Hz), 43.9 (d, CH_2, $J_{C\text{-}P}$ = 1.8 Hz), 52.8 (d, OCH_3, $J_{C\text{-}P}$ = 7.8 Hz), 53.6 (d, OCH_3, $J_{C\text{-}P}$ = 7.1 Hz), 55.1 (s, $PhOCH_3$), 114.2 (d, $2CH_{Ar}$, $J_{C\text{-}P}$ = 2.5 Hz), 126.5 (d, C_{Ar}, $J_{C\text{-}P}$ = 7.3 Hz), 130.0 (d, $2CH_{Ar}$, $J_{C\text{-}P}$ = 6.6 Hz), 159.0 (d, C_{Ar}, $J_{C\text{-}P}$ = 3.0 Hz), 198.7 (d, CHO, $J_{C\text{-}P}$ = 15.7 Hz).

3-(Diphenylphosphoryl)-3-phenylpropanal (**17i**)



Anal. calcd for $C_{21}H_{19}O_2P$: C, 75.44; H, 5.73. Found: C, 75.69; H, 5.81 %.

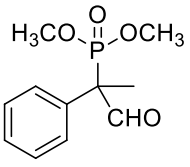
HRMS (EI) calculated for $C_{21}H_{19}O_2P$ 334.11172, found 334.11159.

$^{31}P\{^{1}H\}$ NMR (121 MHz, $CDCl_3$): δ (ppm) = 32.9 (s).

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.98-3.09 (m, 1H, H_A-CH_2), 3.33-3.45 (m, 1H, H_B-CH_2), 4.20-4.27 (m, 1H, CH), 7.18-7.61 (m, 13H, CH-Ar), 7.92-7.99 (m, 2H, CH-Ar), 9.64 (m, 1H, CHO).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 40.0 (d, CH, $J_{C\text{-}P}$ = 68.2 Hz), 43.9 (CH_2), 127.3 (d, CH_{Ar}, $J_{C\text{-}P}$ = 2.4 Hz), 128.0 (CH_{Ar}), 128.2 (CH_{Ar}), 128.4 (CH_{Ar}), 128.5 (CH_{Ar}), 128.8 (CH_{Ar}), 129.0 (CH_{Ar}), 129.7 (CH_{Ar}), 129.7 (CH_{Ar}), 130.5 (d, C_{Ar}, $J_{C\text{-}P}$ = 4.8 Hz), 131.0 (CH_{Ar}), 131.1 (CH_{Ar}), 131.2 (CH_{Ar}), 131.4 (CH_{Ar}), 131.5 (d, CH_{Ar}, $J_{C\text{-}P}$ = 2.7 Hz), 131.8 (C_{Ar}), 132.1 (d, CH_{Ar}, $J_{C\text{-}P}$ = 2.7 Hz), 135.3 (d, C_{Ar}, $J_{C\text{-}P}$ = 5.3 Hz), 198.9 (d, CHO, $J_{C\text{-}P}$ = 13.3 Hz).

Dimethyl (1-oxo-2-phenylpropan-2-yl)phosphonate (**18a**)

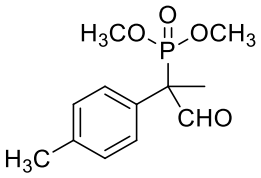


$^{31}P\{^{1}H\}$ NMR (121 MHz, $CDCl_3$): δ (ppm) = 24.7 (s).

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.77 (d, 3H, CH_3, $^{3}J_{H\text{-}P}$ = 15.9 Hz), 3.63 (d, 3H, OCH_3, $^{3}J_{H\text{-}P}$ = 10.8 Hz), 3.72 (d, 3H, OCH_3, $^{3}J_{H\text{-}P}$ = 11.0 Hz), 7.33-7.57 (m, 5H, CH-Ar), 9.84 (d, 1H, CHO, $^{3}J_{H\text{-}P}$ = 4.0 Hz).

^{13}C NMR spectrum could not be analyzed due to the small amount in the final reaction mixture.

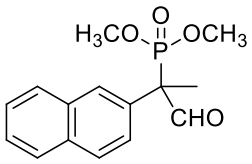
Dimethyl (1-oxo-2-(*p*-tolyl)propan-2-yl)phosphonate (**18b**)



$^{31}P\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ (ppm) = 24.4 (s).

^{1}H and ^{13}C NMR spectra could not be analyzed due to the small amount in the final reaction mixture.

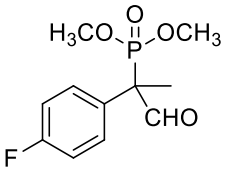
Dimethyl (2-(naphthalene-2-yl)-1-oxopropan-2-yl)phosphonate (**18c**)



$^{31}P\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ (ppm) = 26.1 (s).

^{1}H and ^{13}C NMR spectra could not be analyzed due to the small amount in the final reaction mixture.

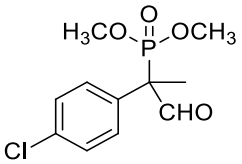
Dimethyl (2-(4-fluorophenyl)-1-oxopropan-2-yl)phosphonate (**18d**)



$^{31}P\{^{1}H\}$ NMR (121 MHz, $CDCl_3$): δ (ppm) = 24.5 (s).

^{1}H and ^{13}C NMR spectra could not be analyzed due to the small amount in the final reaction mixture.

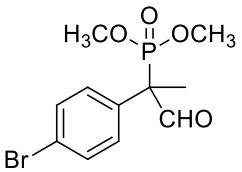
Dimethyl (2-(4-chlorophenyl)-1-oxopropan-2-yl)phosphonate (**18e**)



$^{31}P\{^{1}H\}$ NMR (121 MHz, $CDCl_3$): δ (ppm) = 24.2 (s).

^{1}H and ^{13}C NMR spectra could not be analyzed due to the small amount in the final reaction mixture.

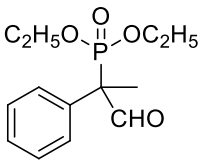
Dimethyl (2-(4-bromophenyl)-1-oxopropan-2-yl)phosphonate (**18f**)



$^{31}P\{^{1}H\}$ NMR (121 MHz, $CDCl_3$): δ (ppm) = 25.5 (s).

^{1}H and ^{13}C NMR spectra could not be analyzed due to the small amount in the final reaction mixture.

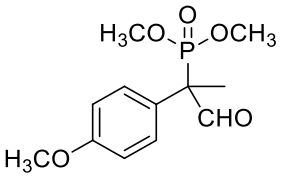
Diethyl (1-oxo-2-phenylpropan-2-yl)phosphonate (**18g**)



$^{31}P\{^{1}H\}$ NMR (121 MHz, $CDCl_3$): δ (ppm) = 24.1 (s).

^{1}H and ^{13}C NMR spectra could not be analyzed due to the small amount in the final reaction mixture.

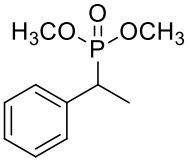
Dimethyl (2-(4-methoxyphenyl)-1-oxopropan-2-yl)phosphonate (**18h**)



$^{31}P\{^{1}H\}$ NMR (121 MHz, $CDCl_3$): δ (ppm) = 25.0 (s).

^{1}H and ^{13}C NMR spectra could not be analyzed due to the small amount in the final reaction mixture.

Dimethyl (1-phenylethyl)phosphonate (**19a**)

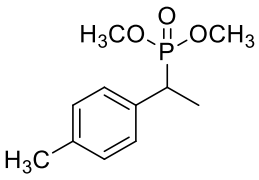


$^{31}P\{^{1}H\}$ NMR (121 MHz, $CDCl_3$): δ (ppm) = 32.1 (s).

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.60 (dd, 3H, CH_3, $^{3}J_{H\text{-}P}$ = 18.6 Hz, $^{3}J_{H\text{-}H}$ = 7.4 Hz), 3.16-3.30 (m, 1H, CH), 3.54 (d, 3H, OCH_3, $^{3}J_{H\text{-}P}$ = 10.5 Hz), 3.69 (d, 3H, OCH_3, $^{3}J_{H\text{-}P}$ = 10.6 Hz), 7.17-7.58 (m, 5H, CH-Ar).

^{13}C NMR spectrum could not be analyzed due to the small amount in the final reaction mixture.

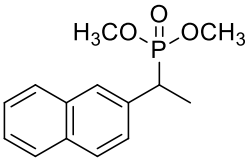
Dimethyl (1-(*p*-tolyl)ethyl)phosphonate (**19b**)



$^{31}P\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ (ppm) = 32.3 (s).

^{1}H and ^{13}C NMR spectra could not be analyzed due to the small amount in the final reaction mixture.

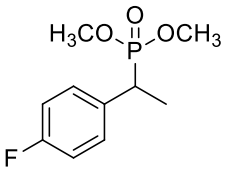
Dimethyl (1-(naphthalene-2-yl)ethyl)phosphonate (**19c**)



$^{31}P\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ (ppm) = 31.9 (s).

^{1}H and ^{13}C NMR spectra could not be analyzed due to the small amount in the final reaction mixture.

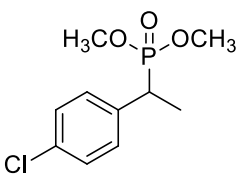
Dimethyl (1-(4-fluorophenyl)ethyl)phosphonate (**19d**)



$^{31}P\{^{1}H\}$ NMR (121 MHz, $CDCl_3$): δ (ppm) = 31.7 (s).

^{1}H and ^{13}C NMR spectra could not be analyzed due to the small amount in the final reaction mixture.

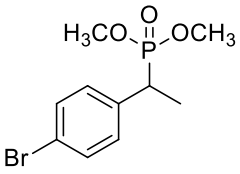
Dimethyl (1-(4-chlorophenyl)ethyl)phosphonate (**19e**)



$^{31}P\{^{1}H\}$ NMR (121 MHz, $CDCl_3$): δ (ppm) = 31.4 (s).

^{1}H and ^{13}C NMR spectra could not be analyzed due to the small amount in the final reaction mixture.

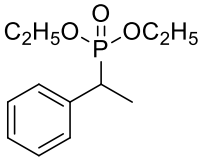
Dimethyl (1-(4-bromophenyl)ethyl)phosphonate (**19f**)



$^{31}P\{^{1}H\}$ NMR (121 MHz, $CDCl_3$): δ (ppm) = 31.2 (s).

^{1}H and ^{13}C NMR spectra could not be analyzed due to the small amount in the final reaction mixture.

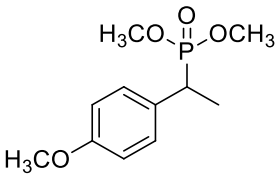
Diethyl (1-phenylethyl)phosphonate (**19g**)



$^{31}P\{^{1}H\}$ NMR (121 MHz, $CDCl_3$): δ (ppm) = 29.7 (s).

^{1}H and ^{13}C NMR spectra could not be analyzed due to the small amount in the final reaction mixture.

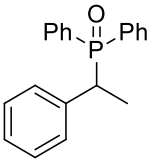
Dimethyl (1-(4-methoxyphenyl)ethyl)phosphonate (**19h**)



$^{31}P\{^{1}H\}$ NMR (121 MHz, $CDCl_3$): δ (ppm) = 32.4 (s).

^{1}H and ^{13}C NMR spectra could not be analyzed due to the small amount in the final reaction mixture.

Diphenyl(1-phenylethyl)phosphine oxide (**19i**)



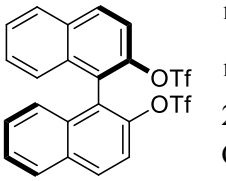
$^{31}P\{^{1}H\}$ NMR (121 MHz, $CDCl_3$): δ (ppm) = 33.6 (s).

^{1}H and ^{13}C NMR spectra could not be analyzed due to the small amount in the final reaction mixture.

5.1.2.6 Synthesis of bidentate phosphorus ligands

Procedure for the synthesis of (*R*)-(1,1'-binaphthalene)-2,2'-diyl bis(trifluoromethanesulfonate) (**20a**)[105]

(*R*)-BINOL (2.00 g, 7.0 mmol) is dissolved in dichloromethane (45 mL) and pyridine (2.0 mL, 25.0 mmol) is added. The solution is cooled to 0 °C and trifluoroacetic anhydride (2.5 mL, 15.0 mmol) is added dropwise. Thus, the mixture is stirred at room temperature for 6 h, concentrated *in vacuo* and dissolved in ethyl acetate (50 mL). The organic layer is washed with 5 % aqueous HCl, saturated $NaHCO_3$-solution and finally with brine (each 10 mL). The organic phase is dried over Na_2SO_4, concentrated *in vacuo* and purified by column chromatography (heptane/dichloromethane = 1:1) to give **20a** as a white solid (3.85 g, 100 %).

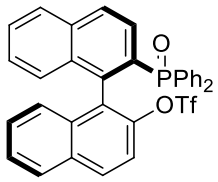


^{19}F NMR (282 MHz, $CDCl_3$): δ (ppm) = -74.6 (s).

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.24-7.27 (m, 2H, CH-Ar), 7.39-7.44 (m, 2H, CH-Ar), 7.56-7.64 (m, 4H, CH-Ar), 8.01 (m, 2H, CH-Ar), 8.15 (m, 2H, CH-Ar).

Procedure for the synthesis of (*R*)-2'-(diphenylphosphoryl)-[1,1'-binaphthalen]-2-yl trifluoromethanesulfonate (**20b**)[105]

In a pressure tube the derivative **20a** (4.80 g, 8.7 mmol), diphenylphosphine oxide (3.52, 17.4 mmol), palladium(II) acetate (99 mg, 0.44 mmol) and dppb (186 mg, 0.44 mmol) are dissolved in dimethyl sulfoxide (40 mL) and Hünig's base (4.51 g, 34.9 mmol) is added in one portion. The solution is heated to 100 °C and stirred for 20 h. After cooling to room temperature, the resulting solution is dissolved in ethyl acetate (50 mL) and washed with water (2×20 mL). The organic layer is dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography (hexane/EtOAc = 1:1) yields **20b** as a white solid (1.73 g, 33 %).



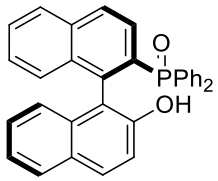
^{19}F NMR (282 MHz, $CDCl_3$): δ (ppm) = -74.6 (s).

$^{31}P\{^1H\}$ NMR (121 MHz, $CDCl_3$): δ (ppm) = 28.1 (s).

^1H NMR (250 MHz, C_6D_6): δ (ppm) = 7.00 (m, CH-Ar), 7.14-8.03 (m, 21H, CH-Ar).

Procedure for the synthesis of (*R*)-(2'-hydroxy-[1,1'-binaphthalen]-2-yl)diphenylphosphine oxide (**20c**)[105]

Phosphine oxide **20b** (520 mg, 0.86 mmol) is dissolved in dioxane:methanol (6 mL, *v*:*v* 2:1) and 3 M NaOH-solution (5 mL) is added. The reaction mixture is stirred at room temperature for 16 h. The resulting solution is acidified with concentrated aqueous HCl to pH = 1 and then extracted with ethyl acetate (2×10 mL). The organic layer is dried over Na_2SO_4, concentrated *in vacuo* and purified by column chromatography (heptane:EtOAc = 1:1) to give **20c** as a white solid (390 mg, 96 %).

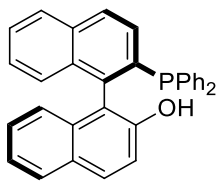


$^{31}P\{^1H\}$ NMR (121 MHz, $CDCl_3$): δ (ppm) = 30.8 (s).

^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 6.43 (m, 1H, CH-Ar), 6.68-7.98 (m, 21H, CH-Ar).

Procedure for the synthesis of (*R*)-2'-(diphenylphosphino)-[1,1'-binaphthalen]-2-ol (**20d**)[105]

Phosphine oxide **20c** (275 mg, 0.58 mmol) is dissolved in toluene (6 mL) and triethylamine is added (431 mg, 4.26 mmol). The solution is cooled to 0 °C and trichlorosilane (402 mg, 2.97 mmol) is added dropwise. The reaction mixture is warmed to 100 °C and stirred for 16 h. After cooling to room temperature, the resulting solution is dissolved in diethyl ether (5 mL) and quenched with a few drops of saturated $NaHCO_3$-solution. The layer is filtrated over Celite, dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography (heptane:EtOAc = 3:1) yields **20d** as a white solid (217 mg, 82 %).



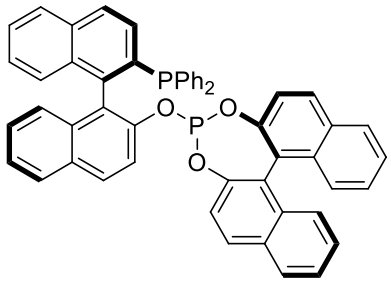
$^{31}P\{^1H\}$ NMR (121 MHz, $CDCl_3$): δ (ppm) = -13.2 (s).

^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 6.75 (d, 1H, CH-Ar), 6.99-7.36 (m, 15H, CH-Ar), 7.45-7.55 (m, 2H, CH-Ar), 7.80 (m, 1H, CH-Ar), 7.89-7.96 (m, 3H, CH-Ar).

General procedure for the synthesis of (*R*,*S*)- and (*R*,*R*)-BINAPHOS **20e,f**

1.05 Eq of enantiopure BINOL are suspended in phosphorus trichloride (1.5 mL/1.0 mmol BINOL), 2-3 drops of *N*-methyl-2-pyrrolidone are added and the solution is heated to 75 °C for 5 min. The resulting HCl gas is derived from the reaction vessel by using a bubble counter (slight argon stream!). The now clear solution is cooled to room temperature, concentrated and dried azeotropically with toluene (three times). Thus, the *in situ* prepared chlorophosphite is dissolved in toluene (5 mL/0.33 mmol BINOL). 1.0 Eq of azeotropically dried phosphine **20d** is dissolved in toluene (5 mL/0.33 mmol substrate) and triethylamine (2.5 eq) is added. This solution is added slowly to the chlorophosphite solution at 0 °C over 5 min and the mixture is kept at this temperature for 5 min. The reaction solution is then stirred at room temperature for 16 h. After this time, it is concentrated *in vacuo* and the residue is purified by column chromatography (alumina, toluene) to give **20e,f** as a white solid.

(*R*,*S*)-BINAPHOS (**20e**)[48]

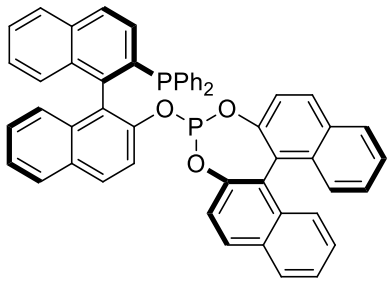


Starting from (*S*)-BINOL (100 mg, 0.35 mmol), phosphine **20d** (150 mg, 0.33 mmol) and Et_3N (88 mg, 0.90 mmol) in toluene (10 mL), the product **20e** was isolated as a white solid (120 mg, 47 %).

$^{31}P\{^1H\}$ NMR (121 MHz, C_6D_6): δ (ppm) = -13.6 (d, PPh_2, $J_{P\text{-}P}$ = 26.4 Hz), 146.4 (d, O-P, $J_{P\text{-}P}$ = 26.4 Hz).

^1H NMR (300 MHz, C_6D_6): δ (ppm) = 6.51-6.54 (m, 1H, CH-Ar), 6.70-7.76 (m, 33H, CH-Ar).

(*R*,*R*)-BINAPHOS (**20f**)[48]



Starting from (*R*)-BINOL (100 mg, 0.35 mmol), phosphine **20d** (150 mg, 0.33 mmol) and Et_3N (88 mg, 0.90 mmol) in toluene (10 mL), the product **20f** was isolated as a white solid (100 mg, 39 %).

$^{31}P\{^1H\}$ NMR (121 MHz, $CDCl_3$): δ (ppm) = -13.4 (d, PPh_2, $J_{P\text{-}P}$ = 9.0 Hz), 145.0 (d, O-P, $J_{P\text{-}P}$ = 9.0 Hz).

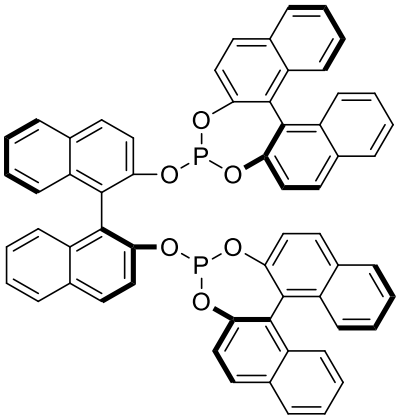
^1H NMR (250 MHz, $CDCl_3$): δ (ppm) = 5.74 (m, 1H, CH-Ar), 6.68-8.03 (m, 33H, CH-Ar).

General procedure for the synthesis of diphosphites **21a-d**

2.1 Eq of enantiopure BINOL are suspended in phosphorus trichloride (1.5 mL/1.0 mmol BINOL), 2-3 drops of *N*-methyl-2-pyrrolidone are added and the solution is heated to 75 °C for 5 min. The resulting HCl gas is derived from the reaction vessel by using a bubble counter (slight argon stream!). The now clear solution is cooled to room temperature, concentrated and dried azeotropically with toluene (three times). Thus, the *in situ* prepared chlorophosphite is dissolved in toluene (10 mL/2.1 mmol BINOL). 1.0 Eq of azeotropically dried aromatic diol is dissolved in toluene (10 mL/1.0 mmol substrate) and triethylamine (5.0 eq) is added. This solution is added slowly to the chlorophosphite solution at 0 °C over 5 min and the mixture is kept at this temperature for 5 min. The reaction solution is then stirred at

room temperature for 16 h. After this time, it is concentrated *in vacuo* and the residue is purified by column chromatography (alumina, toluene) to give **21a-d** as white solids.

(1*S*)-2,2'-Bis[(11b*R*)-dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-yloxy]-1,1'-binaphthalene (**21a**)



Starting from (*R*)-BINOL (601 mg, 2.1 mmol), (*S*)-BINOL (286 mg, 1.0 mmol) and Et_3N (506 mg, 5.0 mmol) in toluene (20 mL), the product **21a** was isolated as a white solid (866 mg, 95 %, R_f 0.90).

Anal. calcd for $C_{60}H_{36}O_6P_2$: C, 78.77; H, 3.97. Found: C, 78.90; H, 4.11 %.

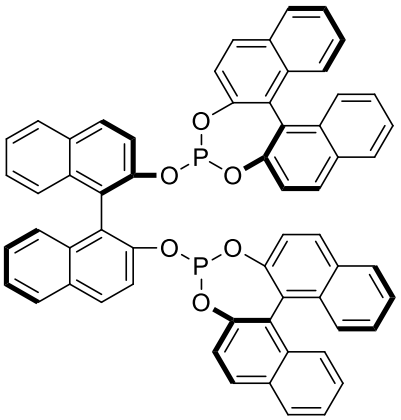
HRMS (EI) calculated for $C_{60}H3_6O_6P_2$ 914.19816, found 914.19795.

$^{31}P\{^1H\}$ NMR (101 MHz, CD_2Cl_2): δ (ppm) = 145.4 (s).

^1H NMR (250 MHz, CD_2Cl_2): δ (ppm) = 5.92 (m, 2H, CH-Ar, $^4J_{H-H}$ = 8.8 Hz), 7.18-8.17 (m, 34H, CH-Ar).

^{13}C NMR (63 MHz, CD_2Cl_2): δ (ppm) = 121.2 ($2CH_{Ar}$), 121.4 ($2CH_{Ar}$), 121.6 ($2CH_{Ar}$), 122.4 ($2C_{Ar}$), 123.0 ($2C_{Ar}$), 124.0 ($2C_{Ar}$), 124.9 ($2CH_{Ar}$), 125.2 ($2CH_{Ar}$), 125.5 ($2CH_{Ar}$), 126.1 ($4CH_{Ar}$), 126.3 ($2CH_{Ar}$), 126.6 ($2CH_{Ar}$), 126.8 ($2CH_{Ar}$), 127.2 ($2CH_{Ar}$), 128.3 ($4CH_{Ar}$), 128.4 ($2CH_{Ar}$), 129.3 ($2CH_{Ar}$), 130.3 ($2CH_{Ar}$), 130.5 ($2CH_{Ar}$), 131.1 ($2C_{Ar}$), 131.3 ($2C_{Ar}$), 131.6 ($2C_{Ar}$), 132.1 ($2C_{Ar}$), 132.7 ($2C_{Ar}$), 134.2 ($2C_{Ar}$), 147.0 ($2C_{Ar}$-O), 147.3 ($2C_{Ar}$-O), 148.3 ($2C_{Ar}$-O).

(1*R*)-2,2'-Bis[(11b*R*)-dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-yloxy]-1,1'-binaphthalene (**21b**)[148]



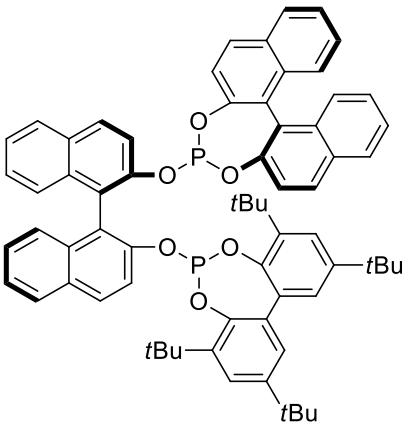
Starting from (*R*)-BINOL (601 mg, 2.1 mmol), (*R*)-BINOL (286 mg, 1.0 mmol) and Et_3N (506 mg, 5.0 mmol) in toluene (20 mL), the product **21b** was isolated as a white solid (848 mg, 93 %, R_f 0.92).

$^{31}P\{^1H\}$ NMR (121 MHz, $CDCl_3$): δ (ppm) = 144.6 (s).

^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 6.45 (m, 2H, CH-Ar, $^4J_{H-H}$ = 8.9 Hz), 7.07-7.35 (m, 22H, CH-Ar), 7.44 (m, 2H, CH-Ar, $^4J_{H-H}$ = 8.9 Hz), 7.64-7.90 (m, 10H, CH-Ar).

^{13}C NMR (63 MHz, $CDCl_3$): δ (ppm) = 121.1 (m, $2CH_{Ar}$), 121.7 ($2CH_{Ar}$), 121.9 ($2CH_{Ar}$), 122.4 (m, $4C_{Ar}$), 124.3 (m, $2C_{Ar}$), 124.6 ($2CH_{Ar}$), 124.9 ($2CH_{Ar}$), 125.1 ($2CH_{Ar}$), 125.8 ($2CH_{Ar}$), 126.1 ($2CH_{Ar}$), 126.2 ($2CH_{Ar}$), 126.8 ($2CH_{Ar}$), 127.0 ($4CH_{Ar}$), 128.1 ($2CH_{Ar}$), 128.2 ($2CH_{Ar}$), 128.4 ($2CH_{Ar}$), 129.5 ($2CH_{Ar}$), 130.0 ($2CH_{Ar}$), 130.3 ($2CH_{Ar}$), 130.8 ($2C_{Ar}$), 131.0 ($2C_{Ar}$), 131.4 ($2C_{Ar}$), 132.3 ($2C_{Ar}$), 132.7 ($2C_{Ar}$), 134.3 ($2C_{Ar}$), 147.0 ($2C_{Ar}$-O), 147.6 (m, $2C_{Ar}$-O), 148.5 (m, $2C_{Ar}$-O).

(11b*R*)-4-{[(*R*)-2'-((2,4,8,10-Tetra-*tert*-butyldibenzo[d,f][1,3,2]dioxaphosphepin-6-yl)oxy)-[1,1'-binaphthalen]-2-yl]oxy}dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine (**21c**)



Starting from (*R*)-BINOL (601 mg, 2.1 mmol), 4,4',6,6'-tetra-*tert*-butyl-2,2'-biphenol (411 mg, 1.0 mmol) and Et_3N (506 mg, 5.0 mmol) in toluene (20 mL), the product **21c** was isolated as a white solid (977 mg, 94 %, R_f 0.91).

$[\alpha]_D^{26}$ = -188.0 (*c* 0.79, $CHCl_3$).

Anal. calcd for $C_{68}H_{64}O_6P_2$: C, 78.59; H, 6.21. Found: C, 78.90; H, 6.42 %.

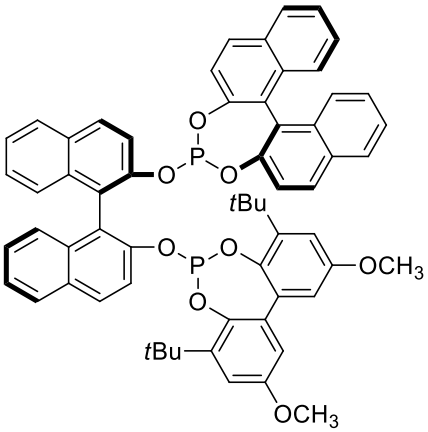
HRMS (EI) calculated for $C_{68}H_{64}O_6P_2$ 1038.41726, found 1038.41702.

$^{31}P\{1H\}$ NMR (101 MHz, CD_2Cl_2): δ (ppm) = 135.2 (s), 144.6 (s).

^{1}H NMR (250 MHz, CD_2Cl_2): δ (ppm) = 1.00 (s, 9H, $C(CH_3)_3$), 1.00 (s, 9H, $C(CH_3)_3$), 1.30 (s, 9H, $C(CH_3)_3$), 1.30 (s, 9H, $C(CH_3)_3$), 6.04 (d, 1H, CH-Ar, *J* = 8.8 Hz), 7.09-7.61 (m, 20H, CH_{Ar}), 7.84-8.12 (m, 7H, CH-Ar).

^{13}C NMR (63 MHz, C_6D_6): δ (ppm) = 31.2 (d, $C(CH_3)_3$, $J_{C\text{-}P}$ = 2.4 Hz), 31.2 (d, $C(CH_3)_3$, $J_{C\text{-}P}$ = 2.8 Hz), 31.6 ($2C(CH_3)_3$), 34.6 ($2C(CH_3)_3$), 35.5 (d, $2C(CH_3)_3$, $J_{C\text{-}P}$ = 6.5 Hz), 121.3 (d, CH_{Ar}, $J_{C\text{-}P}$ = 12.2 Hz), 122.1 (d, CH_{Ar}, $J_{C\text{-}P}$ = 1.0 Hz), 122.4 (CH_{Ar}), 122.6 (d, CH_{Ar}, $J_{C\text{-}P}$ = 9.8 Hz), 123.1 (d, C_{Ar}, $J_{C\text{-}P}$ = 2.5 Hz), 123.2 (d, C_{Ar}, $J_{C\text{-}P}$ = 3.5 Hz), 123.6 (d, C_{Ar}, $J_{C\text{-}P}$ = 2.9 Hz), 124.4 ($2CH_{Ar}$), 125.0 (d, C_{Ar}), 125.0 (CH_{Ar}), 125.2 (CH_{Ar}), 125.3 (CH_{Ar}), 125.5 (CH_{Ar}), 126.3 (CH_{Ar}), 126.6 (CH_{Ar}), 126.8 ($2CH_{Ar}$), 126.9 (CH_{Ar}), 127.0 (CH_{Ar}), 127.2 (CH_{Ar}), 127.3 (CH_{Ar}), 127.4 (CH_{Ar}), 127.5 (CH_{Ar}), 128.3 ($2CH_{Ar}$), 128.5 (CH_{Ar}), 128.6 (CH_{Ar}), 129.9 (CH_{Ar}), 129.9 (CH_{Ar}), 130.2 (CH_{Ar}), 130.6 (CH_{Ar}), 131.4 (C_{Ar}), 131.4 (C_{Ar}), 131.7 (C_{Ar}), 132.0 (C_{Ar}), 133.1 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.4 Hz), 133.4 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.4 Hz), 133.7 (d, C_{Ar}, $J_{C\text{-}P}$ = 4.0 Hz), 133.8 (d, C_{Ar}, $J_{C\text{-}P}$ = 4.0 Hz), 134.8 (C_{Ar}), 134.9 (C_{Ar}), 141.1 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.5 Hz), 141.2 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.4 Hz), 146.2 (d, C_{Ar}, $J_{C\text{-}P}$ = 3.5 Hz), 146.3 (d, C_{Ar}, $J_{C\text{-}P}$ = 3.0 Hz), 146.8 ($2C_{Ar}$), 147.8 (d, C_{Ar}, $J_{C\text{-}P}$ = 2.0 Hz), 148.6 (d, C_{Ar}, $J_{C\text{-}P}$ = 5.5 Hz), 148.7 (C_{Ar}), 149.0 (d, C_{Ar}, $J_{C\text{-}P}$ = 7.1 Hz).

(11b*R*)-4-{[(*R*)-2'-((4,8-Di-*tert*-butyl-2,10-dimethoxydibenzo[*d*,*f*][1,3,2]dioxaphosphepin-6-yl)oxy)-[1,1'-binaphthalen]-2-yl]oxy}dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine (**21d**)



Starting from (*R*)-BINOL (601 mg, 2.1 mmol), 4,4'-di-methoxy-6,6'-di-*tert*-butyl-2,2'-biphenol (359 mg, 1.0 mmol) and Et_3N (506 mg, 5.0 mmol) in toluene (20 mL), the product **21d** was isolated as a white solid (961 mg, 97 %, R_f 0.92).

$[\alpha]_D^{26}$ = -132.1 (*c* 0.54, $CHCl_3$).

Anal. calcd for $C_{62}H_{52}O_8P_2$: C, 75.45; H, 5.31. Found: C, 75.27; H, 5.04 %.

HRMS (EI) calculated for $C_{62}H_{52}O_8P_2$ 986.31319, found 986.31301.

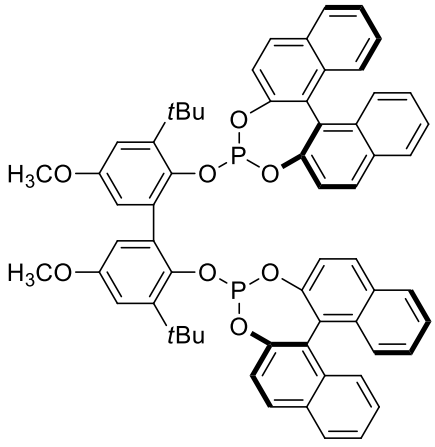
$^{31}P\{1H\}$ NMR (121 MHz, $CDCl_3$): δ (ppm) = 138.5 (s), 144.5 (s).

^{1}H NMR (300 MHz, CD_2Cl_2): δ (ppm) = 0.97 (s, 9H, C(CH_3)$_3$), 1.03 (s, 9H, C(CH_3)$_3$), 3.72 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 6.10 (d, 1H, CH-Ar, *J* = 6.1 Hz), 6.54 (dd, 2H, CH-Ar, *J* = 5.1 Hz, *J* = 3.1 Hz), 6.78 (dd, 2H, CH-Ar, *J* = 6.5 Hz, *J* = 3.1 Hz), 7.13-7.49 (m, 14H, CH_{Ar}), 7.58 (d, 1H, CH-Ar, *J* = 8.9 Hz), 7.67 (dd, 1H, CH-Ar, *J* = 8.9 Hz, *J* = 1.0 Hz), 7.84-7.95 (m, 5H, CH-Ar), 8.03 (d, 1H, CH-Ar, *J* = 8.3 Hz), 8.12 (d, 1H, CH-Ar, *J* = 8.9 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 30.5 (d, C(*C*H_3)$_3$, $J_{C\text{-}P}$ = 2.1 Hz), 30.6 (d, C(*C*H_3)$_3$, $J_{C\text{-}P}$ = 2.8 Hz), 34.9 (*C*(CH_3)$_3$), 35.0 (*C*(CH_3)$_3$), 55.5 (2OCH_3), 112.4 (CH_{Ar}), 112.5 (CH_{Ar}), 113.9 (CH_{Ar}), 114.2 (CH_{Ar}), 120.8 (d, CH_{Ar}, $J_{C\text{-}P}$ = 10.7 Hz), 121.4 (d, CH_{Ar}, $J_{C\text{-}P}$ = 10.9 Hz), 121.8 (2CH_{Ar}), 122.3 (d, C_{Ar}, $J_{C\text{-}P}$ = 2.6 Hz), 122.5 (d, C_{Ar}, $J_{C\text{-}P}$ = 3.5 Hz), 122.6 (d, C_{Ar}, $J_{C\text{-}P}$ = 3.1 Hz), 124.1 (d, C_{Ar}, $J_{C\text{-}P}$ = 5.1 Hz), 124.6 (CH_{Ar}), 124.8 (CH_{Ar}), 125.0 (CH_{Ar}), 125.1 (CH_{Ar}), 125.8 (CH_{Ar}), 126.1 (CH_{Ar}), 126.2 (CH_{Ar}), 126.3 (CH_{Ar}), 126.5 (CH_{Ar}), 126.8 (CH_{Ar}), 126.9 (CH_{Ar}), 127.0 (CH_{Ar}), 127.9 (CH_{Ar}), 128.0 (CH_{Ar}), 128.2 (2CH_{Ar}), 129.4 (CH_{Ar}), 129.6 (CH_{Ar}), 129.7 (CH_{Ar}), 130.1 (CH_{Ar}), 130.7 (C_{Ar}), 130.8 (C_{Ar}), 131.1 (C_{Ar}), 131.5 (C_{Ar}), 132.4 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.4 Hz), 132.8 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.1 Hz), 133.3 (d, C_{Ar}, $J_{C\text{-}P}$ = 4.0 Hz), 133.5 (d, C_{Ar}, $J_{C\text{-}P}$ = 4.0 Hz), 134.0 (C_{Ar}), 134.3 (C_{Ar}), 141.3 (d, C_{Ar}), 141.4 (d, C_{Ar}), 142.7 (2C_{Ar}) 147.1 (d, C_{Ar}, $J_{C\text{-}P}$ = 2.3 Hz), 147.7 (d, C_{Ar}, $J_{C\text{-}P}$ = 4.9 Hz), 148.0 (d, C_{Ar}, $J_{C\text{-}P}$ = 7.8 Hz), 148.2 (C_{Ar}), 155.4 (2C_{Ar}).

Procedure for the synthesis of (11b*R*,11c'*R*)-4,4'-[(3,3'-Di-*tert*-butyl-5,5'-dimethoxy-[1,1'-biphenyl]-2,2'-diyl)bis(oxy)]didinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine (**21e**)

294 mg (1.02 mmol) of (*R*)-BINOL are suspended in phosphorus trichloride (1.5 mL), 2-3 drops of *N*-methyl-2-pyrrolidone are added and the solution is heated to 75 °C for 5 min. The resulting HCl gas is derived from the reaction vessel by using a bubble counter (slight argon stream!). The now clear solution is cooled to room temperature, concentrated and dried azeotropically with toluene (three times). Thus, the *in situ* prepared chlorophosphite is dissolved in toluene (3 mL). 180 mg (0.5 mmol) of azeotropically dried 4,4'-di-methoxy-6,6'-di-*tert*-butyl-2,2'-biphenol is dissolved in toluene (2 mL) and the solution is cooled to -20 °C. *n*-BuLi (1.6 M in hexane, 0.63 mL, 1.0 mmol) is added and the mixture is warmed to room temperature over 30 min and stirred for futher 90 min. This solution is added slowly to the chlorophosphite solution and stirred at room temperature for 16 h. After this time, it is concentrated *in vacuo* and the residue is purified by column chromatography (alumina, toluene) to give 300 mg of **21e** as a white solid (61 %, R_f 0.93).



$[\alpha]_D^{25}$ = -106.1 (*c* 0.59, $CHCl_3$).

Anal. calcd for $C_{62}H_{52}O_8P_2$: C, 75.45; H, 5.31. Found: C, 75.12; H, 5.22 %.

HRMS (EI) calculated for $C_{62}H_{52}O_8P_2$ 986.31319, found 986.31299.

^{31}P{1H} NMR (101 MHz, C_6D_6): δ (ppm) = 146.4 (s), 146.5 (s).

^{1}H NMR (250 MHz, C_6D_6): δ (ppm) = 1.33 (s, 9H, C(CH_3)$_3$), 1.63 (s, 9H, C(CH_3)$_3$), 3.25 (s, 3H, OCH_3), 3.54 (s, 3H, OCH_3), 6.83-7.70 (m, 28H, CH-Ar).

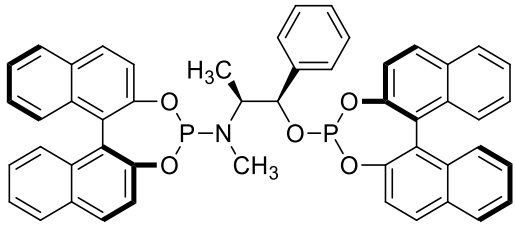
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 30.4 (C(*C*H_3)$_3$), 31.1 (C(*C*H_3)$_3$), 35.5 (*C*(CH_3)$_3$), 36.0 (*C*(CH_3)$_3$), 55.2 (OCH_3), 55.4 (OCH_3), 114.7 (CH_{Ar}), 115.8 (CH_{Ar}), 116.4 (2CH_{Ar}), 122.2 (CH_{Ar}), 122.3 (2CH_{Ar}), 123.7 (CH_{Ar}), 124.9 (CH_{Ar}), 124.9 (d, C_{Ar}), 125.0 (d, C_{Ar}), 125.1 (CH_{Ar}), 125.2 (CH_{Ar}), 125.2 (d, C_{Ar}), 125.2 (C_{Ar}), 125.3 (CH_{Ar}), 126.2 (CH_{Ar}), 126.4

(CH_{Ar}), 126.5 (CH_{Ar}), 126.6 (CH_{Ar}), 127.5 ($2CH_{Ar}$), 127.6 (CH_{Ar}), 127.6 (CH_{Ar}), 128.6 (CH_{Ar}), 128.7 ($3CH_{Ar}$), 129.6 (CH_{Ar}), 130.1 (CH_{Ar}), 130.5 (CH_{Ar}), 130.6 (CH_{Ar}), 131.6 (C_{Ar}), 131.4 (C_{Ar}), 132.0 (C_{Ar}), 132.1 (C_{Ar}), 133.0 (C_{Ar}), 133.1 (d, C_{Ar}), 133.1 (C_{Ar}), 133.3 (C_{Ar}), 133.4 ($2C_{Ar}$), 143.9 (C_{Ar}), 144.1 (C_{Ar}), 144.6 (m, C_{Ar}) 145.4 (m, C_{Ar}), 147.7 (C_{Ar}), 147.8 (C_{Ar}), 148.9 (m, C_{Ar}), 149.2 (m, C_{Ar}), 155.6 (C_{Ar}), 155.8 (C_{Ar}).

General procedure for the synthesis of 1,2-amino alcohol-based phosphites-phosphoramidites **22a-e**

2.1 Eq of enantiopure BINOL are suspended in phosphorus trichloride (1.5 mL/1.0 mmol BINOL), 2-3 drops of *N*-methyl-2-pyrrolidone are added and the solution is heated to 75 °C for 5 min. The resulting HCl gas is derived from the reaction vessel by using a bubble counter (slight argon stream!). The now clear solution is cooled to room temperature, concentrated and dried azeotropically with toluene (three times). Thus, the *in situ* prepared chlorophosphite is dissolved in toluene (10 mL/2.1 mmol BINOL). 1.0 Eq of azeotropically dried amino alcohol is dissolved in toluene (10 mL/1.0 mmol substrate) and triethylamine (5.0 eq) is added. This solution is added slowly to the chlorophosphite solution at 0 °C over 5 min and the mixture is kept at this temperature for 5 min. The reaction solution is then stirred at room temperature for 16 h. After this time, it is concentrated *in vacuo* and the residue is purified by column chromatography (alumina, toluene) to give **22a-e** as a white solid.

(11b*S*)-*N*-{(1*R*,2*S*)-1-[(11b*S*)-Dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-yloxy]-1-phenylpropan-2-yl}-*N*-methyldinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-amine (**22a**)



Starting from (*S*)-BINOL (601 mg, 2.1 mmol), (1*R*,2*S*)-(–)-ephedrine (165 mg, 1.0 mmol) and Et_3N (506 mg, 5.0 mmol) in toluene (20 mL), the product **22a** was isolated as a white solid (412 mg, 52 %, R_f 0.90).

$[\alpha]_D^{23}$ = +292.6 (*c* 0.70, $CHCl_3$).

Anal. calcd for $C_{50}H_{37}NO_5P_2$: C, 75.66; H, 4.70; N, 1.76. Found: C, 75.64; H, 5.08; N, 1.96 %.

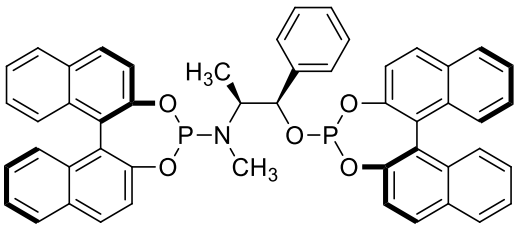
HRMS (EI) calculated for $C_{50}H_{37}NO_5P_2$ 793.21415, found 793.21325.

$^{31}P\{^1H\}$ NMR (121 MHz, $CDCl_3$): δ (ppm) = 142.7 (s), 148.5 (s).

^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.50 (d, 3H, CHC*H*$_3$, $^3J_{H-H}$ = 6.7 Hz), 2.14 (d, 3H, NCH_3, $^3J_{H-P}$ = 4.0 Hz), 3.77-3.91 (m, 1H, C*H*CH_3), 5.18 (dd, 1H, CHPh, $^3J_{H-P}$ = 8.3 Hz, $^3J_{H-H}$ = 8.3 Hz), 6.97-7.95 (m, 29H, CH-Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 16.1 (d, CH*C*H_3, J_{C-P} = 6.3 Hz), 27.6 (d, NCH_3, J_{C-P} = 1.3 Hz), 58.4 (dd, *C*HCH_3, J_{C-P} = 41.7 Hz, J_{C-P} = 4.6 Hz), 79.1 (dd, CHPh, J_{C-P} = 6.1 Hz, J_{C-P} = 6.0 Hz), 121.8 (CH_{Ar}), 121.9 ($3CH_{Ar}$), 122.4 (d, C_{Ar}, J_{C-P} = 2.1 Hz), 123.8 (d, C_{Ar}, J_{C-P} = 4.7 Hz), 124.3 (d, C_{Ar}, J_{C-P} = 5.3 Hz), 124.5 (CH_{Ar}), 124.7 (CH_{Ar}), 124.7 (d, C_{Ar}), 124.8 (CH_{Ar}), 125.1 (CH_{Ar}), 126.0 (CH_{Ar}), 126.0 (CH_{Ar}), 126.1 (CH_{Ar}), 126.2 (CH_{Ar}), 126.9 (CH_{Ar}), 127.0 (CH_{Ar}), 127.0 (CH_{Ar}), 127.1 (CH_{Ar}), 127.4 ($2CH_{Ar}$), 128.2 (CH_{Ar}), 128.2 ($2CH_{Ar}$), 128.3 ($3CH_{Ar}$), 128.4 (CH_{Ar}), 129.7 (CH_{Ar}), 129.9 (CH_{Ar}), 130.1 (CH_{Ar}), 130.3 (CH_{Ar}), 130.6 (C_{Ar}), 130.9 (C_{Ar}), 131.3 (C_{Ar}), 131.6 (C_{Ar}), 132.5 (d, C_{Ar}), 132.5 (d, C_{Ar}), 132.7 (d, C_{Ar}, J_{C-P} = 1.6 Hz), 132.8 (C_{Ar}, J_{C-P} = 1.7 Hz), 139.5 (C_{Ar}), 147.4 (d, C_{Ar}-O, J_{C-P} = 1.3 Hz), 148.2 (d, C_{Ar}-O, J_{C-P} = 5.4 Hz), 149.3 (C_{Ar}-O), 150.2 (d, C_{Ar}-O, J_{C-P} = 5.0 Hz).

(11b*R*)-*N*-{(1*R*,2*S*)-1-[(11b*R*)-Dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-yloxy]-1-phenylpropan-2-yl}-*N*-methyldinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-amine (**22b**)



Starting from (*R*)-BINOL (601 mg, 2.1 mmol), (1*R*,2*S*)-(–)-ephedrine (165 mg, 1.0 mmol) and Et_3N (506 mg, 5.0 mmol) in toluene (20 mL), the product **22b** was isolated as a white solid (518 mg, 65 %, R_f 0.89).

$[\alpha]_D^{23}$ = -290.0 (*c* 0.70, $CHCl_3$).

Anal. calcd for $C_{50}H_{37}NO_5P_2$: C, 75.66; H, 4.70; N, 1.76. Found: C, 75.56; H, 4.96; N, 1.78 %.

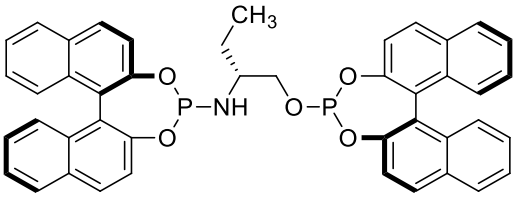
HRMS (EI) calculated for $C_{50}H_{37}NO_5P_2$ 793.21415, found 793.21271.

$^{31}P\{^1H\}$ NMR (101 MHz, C_6D_6): δ (ppm) = 141.5 (s), 143.9 (s).

^1H NMR (250 MHz, C_6D_6): δ (ppm) = 1.22 (d, 3H, CHC*H*$_3$, $^3J_{H-H}$ = 6.8 Hz), 2.21 (d, 3H, NCH_3, $^3J_{H-P}$ = 6.1 Hz), 3.86-4.02 (m, 1H, C*H*CH_3), 5.48 (dd, 1H, CHPh, $^3J_{H-P}$ = 9.9 Hz, $^3J_{H-H}$ = 6.6 Hz), 6.85-7.66 (m, 29H, CH-Ar).

^{13}C NMR (63 MHz, C_6D_6): δ (ppm) = 14.8 (d, CH*C*H$_3$, J_{C-P} = 5.8 Hz), 28.5 (d, NCH_3, J_{C-P} = 7.9 Hz), 58.3 (dd, *C*HCH$_3$, J_{C-P} = 35.3 Hz, J_{C-P} = 5.0 Hz), 81.7 (dd, CHPh, J_{C-P} = 17.5 Hz, J_{C-P} = 4.9 Hz), 122.2 (d, CH_{Ar}, J_{C-P} = 1.3 Hz), 122.4 (d, CH_{Ar}, J_{C-P} = 1.1 Hz), 122.7 ($2CH_{Ar}$), 122.9 (d, C_{Ar}, J_{C-P} = 2.3 Hz), 123.6 (d, C_{Ar}, J_{C-P} = 2.6 Hz), 124.5 (d, C_{Ar}, J_{C-P} = 5.0 Hz), 124.8 (CH_{Ar}), 125.0 (d, C_{Ar}), 125.0 (CH_{Ar}), 125.2 (CH_{Ar}), 125.3 (CH_{Ar}), 126.5 (CH_{Ar}), 126.5 (CH_{Ar}), 126.6 (CH_{Ar}), 126.7 (CH_{Ar}), 127.4 ($3CH_{Ar}$), 127.5 (CH_{Ar}), 128.0 ($2CH_{Ar}$), 128.5 ($3CH_{Ar}$), 128.7 ($4CH_{Ar}$), 129.8 (CH_{Ar}), 130.0 (CH_{Ar}), 130.8 (CH_{Ar}), 130.8 (CH_{Ar}), 131.1 (C_{Ar}), 131.6 (C_{Ar}), 131.9 (C_{Ar}), 132.1 (C_{Ar}), 133.2 (d, C_{Ar}), 133.2 (d, C_{Ar}), 133.4 (d, C_{Ar}, J_{C-P} = 1.4 Hz), 133.5 (d, C_{Ar}, J_{C-P} = 1.6 Hz), 140.1 (d, C_{Ar}, J_{C-P} = 0.9 Hz), 148.1 (d, C_{Ar}-O, J_{C-P} = 2.1 Hz), 148.7 (d, C_{Ar}-O, J_{C-P} = 4.9 Hz), 150.2 (d, C_{Ar}-O, J_{C-P} = 0.8 Hz), 150.8 (d, C_{Ar}-O, J_{C-P} = 6.4 Hz).

(11b*R*)-*N*-{(2*R*)-1-[(11b*R*)-Dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-yloxy]butan-2-yl}dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-amine (**22c**)



Starting from (*R*)-BINOL (601 mg, 2.1 mmol), (*R*)-(–)-2-amino-1-butanol (89 mg, 1.0 mmol) and Et_3N (506 mg, 5.0 mmol) in toluene (20 mL), the product **22c** was isolated as a white solid (200 mg, 28 %, R_f 0.92).

$[\alpha]_D^{24}$ = -492.5 (*c* 0.45, $CHCl_3$).

HRMS (EI) calculated for $C_{44}H_{33}NO_5P_2$ 717.18285, found 717.18320.

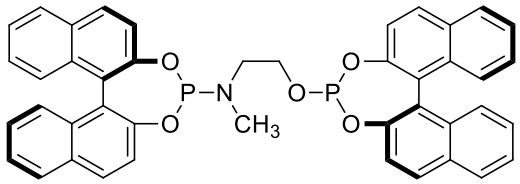
$^{31}P\{^1H\}$ (121 MHz, C_6D_6): δ (ppm) = 138.8 (s), 151.4 (s).

^1H NMR (300 MHz, C_6D_6): δ (ppm) = 0.70 (t, 3H, CH_3, $^3J_{H-H}$ = 7.4 Hz), 1.06-1.26 (m, 2H, CH_2), 2.92-3.04 (m, 1H, C*H*CH_2), 3.40 (ddd, 1H, H_A-CH_2, $^2J_{A-B}$ = 10.0 Hz, *J* = 5.3 Hz, *J* = 4.3 Hz), 3.79 (ddd, 1H, H_B-CH_2, $^2J_{A-B}$ = 10.1 Hz, *J* = 7.2 Hz, *J* = 4.3 Hz), 6.89-7.65 (m, 24H, CH-Ar).

^{13}C NMR (63 MHz, C_6D_6): δ (ppm) = 10.4 (CH_3), 27.0 (d, CH*C*H$_2$, J_{C-P} = 3.8 Hz), 53.1 (dd, *C*HCH$_2$, J_{C-P} = 19.7 Hz, J_{C-P} = 4.7 Hz), 68.8 (dd, CH_2, J_{C-P} = 3.7 Hz, J_{C-P} = 1.5 Hz), 122.1 (CH_{Ar}), 122.2 (d, CH_{Ar}, J_{C-P} = 1.7 Hz), 122.3 (d, CH_{Ar}, J_{C-P} = 1.7 Hz), 122.8 (CH_{Ar}), 123.4 (d, C_{Ar}, J_{C-P} = 2.5 Hz), 124.2 (d, C_{Ar}, J_{C-P} = 2.4 Hz), 124.6 (d, C_{Ar}, J_{C-P} = 5.3 Hz), 124.7 (d, C_{Ar}, J_{C-P} = 4.9 Hz), 125.0 (CH_{Ar}), 125.0

(CH_{Ar}), 125.2 (CH_{Ar}), 125.3 (CH_{Ar}), 126.5 (CH_{Ar}), 126.6 (CH_{Ar}), 126.7 (CH_{Ar}), 126.8 (CH_{Ar}), 127.4 ($4CH_{Ar}$), 128.6 (CH_{Ar}), 128.7 (CH_{Ar}), 128.7 (CH_{Ar}), 128.8 (CH_{Ar}), 129.8 (CH_{Ar}), 130.5 (CH_{Ar}), 130.8 (CH_{Ar}), 131.0 (CH_{Ar}), 131.4 (C_{Ar}), 131.5 (C_{Ar}), 132.0 (d, C_{Ar}, $J_{C\text{-}P}$ = 0.8 Hz), 132.1 (C_{Ar}), 133.3 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.4 Hz), 133.4 (d, $3C_{Ar}$, $J_{C\text{-}P}$ = 1.1 Hz), 148.2 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 2.1 Hz), 148.6 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 5.2 Hz), 149.6 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 5.1 Hz), 150.3 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 1.5 Hz).

(11b*R*)-*N*-{2-[(11b*R*)-Dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-yloxy]ethyl}-*N*-methyldinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-amine (**22d**)



Starting from (*R*)-BINOL (601 mg, 2.1 mmol), 2-(methylamino)ethanol (75 mg, 1.0 mmol) and Et_3N (506 mg, 5.0 mmol) in toluene (20 mL), the product **22d** was isolated as a white solid (250 mg, 36 %, R_f 0.84).

$[\alpha]_D^{24}$ = -506.7 (*c* 0.72, $CHCl_3$).

Anal. calcd for $C_{43}H_{31}NO_5P_2$: C, 73.40; H, 4.44; N, 1.99. Found: C, 73.35; H, 3.51; N, 2.21 %.

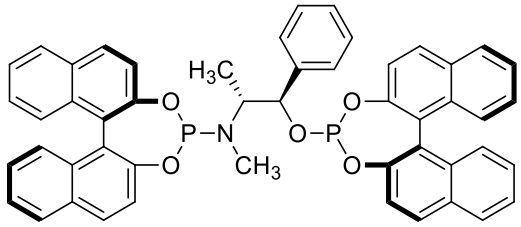
HRMS (EI) calculated for $C_{43}H_{31}NO_5P_2$ 703.16720, found 703.16781.

$^{31}P\{^1H\}$ (121 MHz, C_6D_6): δ (ppm) = 138.5 (s), 149.4 (s).

^1H NMR (300 MHz, C_6D_6): δ (ppm) = 2.16 (d, 3H, CH_3, $^3J_{H\text{-}P}$ = 5.4 Hz), 2.60-2.74 (m, 1H, CH_2), 3.06-3.18 (m, 1H, CH_2), 3.44-3.53 (m, 1H, CH_2), 3.71-3.81 (m, 1H, CH_2), 6.90-7.69 (m, 24H, CH-Ar).

^{13}C NMR (63 MHz, C_6D_6): δ (ppm) = 32.6 (d, CH_3, $J_{C\text{-}P}$ = 4.6 Hz), 50.2 (dd, NCH_2), 62.8 (brs, OCH_2), 122.2 (CH_{Ar}), 122.2 (d, CH_{Ar}, $J_{C\text{-}P}$ = 1.5 Hz), 122.4 (d, CH_{Ar}, $J_{C\text{-}P}$ = 1.4 Hz), 122.7 (CH_{Ar}), 123.3 (d, C_{Ar}, $J_{C\text{-}P}$ = 2.6 Hz), 123.4 (d, C_{Ar}, $J_{C\text{-}P}$ = 2.2 Hz), 124.6 (d, C_{Ar}), 124.7 (d, C_{Ar}), 124.9 (CH_{Ar}), 125.0 (CH_{Ar}), 125.3 (CH_{Ar}), 125.3 (CH_{Ar}), 126.5 (CH_{Ar}), 126.6 (CH_{Ar}), 126.8 ($2CH_{Ar}$), 127.4 ($4CH_{Ar}$), 128.6 (CH_{Ar}), 128.7 (CH_{Ar}), 128.8 (CH_{Ar}), 128.8 (CH_{Ar}), 130.4 (CH_{Ar}), 130.5 (CH_{Ar}), 130.8 (CH_{Ar}), 131.0 (CH_{Ar}), 131.3 (C_{Ar}), 131.5 (C_{Ar}), 132.0 (C_{Ar}), 132.1 (C_{Ar}), 133.3 (d, C_{Ar}), 133.3 (C_{Ar}), 133.5 (C_{Ar}), 133.5 (C_{Ar}), 148.3 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 2.3 Hz), 149.7 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 5.3 Hz), 150.2 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 0.8 Hz), 150.8 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 5.7 Hz).

(11b*R*)-*N*-{(1*R*,2*R*)-1-[(11b*R*)-Dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-yloxy]-1-phenylpropan-2-yl}-*N*-methyldinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-amine (**22e**)



Starting from (*R*)-BINOL (601 mg, 2.1 mmol), (1*R*,2*R*)-(–)-pseudoephedrine (165 mg, 1.0 mmol) and Et_3N (506 mg, 5.0 mmol) in toluene (20 mL), the product **22e** was isolated as a white solid (640 mg, 81 %, R_f 0.90).

$[\alpha]_D^{25}$ = -89.7 (*c* 0.63, $CHCl_3$).

HRMS (EI) calculated for $C_{50}H_{37}NO_5P_2$ 793.21415, found 793.21475.

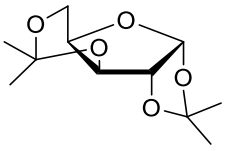
$^{31}P\{^1H\}$ (121 MHz, C_6D_6): δ (ppm) = 138.4 (s), 145.0 (s).

^1H NMR (250 MHz, C_6D_6): δ (ppm) = 0.52 (d, 3H, CHC*H*$_3$, $^3J_{H\text{-}H}$ = 6.1 Hz), 1.50 (d, 3H, NCH_3, $^3J_{H\text{-}P}$ = 14.4 Hz), 2.75-2.87 (m, 1H, C*H*CH_3), 4.50 (dd, 1H, CHPh, $^3J_{H\text{-}P}$ = 9.5 Hz, $^3J_{H\text{-}H}$ = 3.1 Hz), 6.71-7.95 (m, 29H, CH-Ar).

^{13}C NMR (63 MHz, C_6D_6): δ (ppm) = 14.4 (d, CH*C*H$_3$, $J_{C\text{-}P}$ = 7.0 Hz), 27.9 (d, NCH$_3$, $J_{C\text{-}P}$ = 12.9 Hz), 61.5 (d, *C*HCH$_3$, $J_{C\text{-}P}$ = 6.0 Hz), 92.6 (d, CHPh, $J_{C\text{-}P}$ = 10.1 Hz), 121.0 (d, CH$_{Ar}$, $J_{C\text{-}P}$ = 14.1 Hz), 121.9 (d, CH$_{Ar}$, $J_{C\text{-}P}$ = 6.7 Hz), 122.0 (d, C$_{Ar}$, $J_{C\text{-}P}$ = 1.8 Hz), 122.5 (CH$_{Ar}$), 123.3 (d, C$_{Ar}$, $J_{C\text{-}P}$ = 2.2 Hz), 124.8 (CH$_{Ar}$), 124.8 (d, C$_{Ar}$), 125.0 (CH$_{Ar}$), 125.0 (d, C$_{Ar}$, $J_{C\text{-}P}$ = 5.2 Hz), 125.2 (CH$_{Ar}$), 125.4 (CH$_{Ar}$), 126.1 (CH$_{Ar}$), 126.3 (d, CH$_{Ar}$, $J_{C\text{-}P}$ = 1.6 Hz), 126.6 (CH$_{Ar}$), 126.9 (CH$_{Ar}$), 127.3 (2CH$_{Ar}$), 127.3 (CH$_{Ar}$), 127.5 (CH$_{Ar}$), 128.2 (CH$_{Ar}$), 128.2 (CH$_{Ar}$), 128.2 (2CH$_{Ar}$), 128.5 (CH$_{Ar}$), 128.6 (4CH$_{Ar}$), 128.7 (CH$_{Ar}$), 129.8 (CH$_{Ar}$), 130.0 (CH$_{Ar}$), 130.6 (CH$_{Ar}$), 130.7 (CH$_{Ar}$), 131.0 (C$_{Ar}$), 131.5 (C$_{Ar}$), 131.7 (C$_{Ar}$), 132.0 (C$_{Ar}$), 133.0 (d, C$_{Ar}$, $J_{C\text{-}P}$ = 1.4 Hz), 133.4 (d, C$_{Ar}$, $J_{C\text{-}P}$ = 1.4 Hz), 134.8 (C$_{Ar}$) 135.0 (C$_{Ar}$), 139.6 (C$_{Ar}$), 147.7 (d, C$_{Ar}$-O, $J_{C\text{-}P}$ = 2.3 Hz), 148.4 (d, C$_{Ar}$-O, $J_{C\text{-}P}$ = 4.9 Hz), 148.8 (d, C$_{Ar}$-O, $J_{C\text{-}P}$ = 7.2 Hz), 151.4 (d, C$_{Ar}$-O, $J_{C\text{-}P}$ = 5.7 Hz).

Procedure for the synthesis of (–)-1,2:3,5-di-*O*-isopropylidene-α-D-xylofuranose (**23a**)[149]

D-(+)-Xylose (1.5 g, 10.0 mmol) is dissolved in acetone (90 mL) and iodine is added (450 mg, 1.8 mmol). The reaction mixture is stirred at room temperature for 16 h. After this time, saturated $Na_2S_2O_3$-solution is added until the mixture becomes colorless to yellowish. The organic solvent is removed *in vacuo* and the residue is extracted with dichloromethane (3×20 mL) and dried over Na_2SO_4. Concentration *in vacuo* yields 2.21 g of **23a** (96 %) as a yellowish solid.

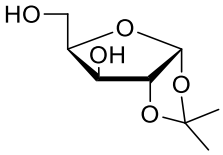


^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.32 (s, 3H, C(CH$_3$)$_2$), 1.37 (s, 3H, C(CH$_3$)$_2$), 1.43 (s, 3H, C(CH$_3$)$_2$), 1.49 (s, 3H, C(CH$_3$)$_2$), 4.00-4.11 (m, 3H, H-4 and 2H-5), 4.31 (d, 1H, H-3, J = 2.5 Hz), 4.52 (d, 1H, H-2, $^3J_{1\text{-}2}$ = 3.7 Hz), 6.02 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.8 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 18.7 (C(*C*H$_3$)$_2$), 26.2 (C(*C*H$_3$)$_2$), 26.8 (C(*C*H$_3$)$_2$), 28.7 (C(*C*H$_3$)$_2$), 60.0 (C-5), 71.6 (C-3), 73.2 (C-4), 84.4 (C-2), 97.5 (*C*(CH$_3$)$_2$), 105.1 (C-1), 111.6 (*C*(CH$_3$)$_2$).

Procedure for the synthesis of 1,2-*O*-(methylethylidene)-α-D-xylofuranose (**23b**)[149]

Protected α-D-xylose **23a** (2.0 g, 8.7 mmol) is dissolved in methanol (12 mL) and aqueous H_2SO_4-solution is added (0.8 %, 12 mL). The reaction mixture is stirred at room temperature for 16 h. After this time, solid $BaCO_3$ is added to neutralize the mixture. The solution is filtrated over Celite and then washed with methanol and ethyl acetate. Concentration *in vacuo* yields 1.52 g of **23b** (92 %) as a yellowish, viscous oil.



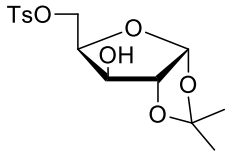
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.32 (s, 3H, C(CH$_3$)$_2$), 1.49 (s, 3H, C(CH$_3$)$_2$), 3.97-4.11 (m, 2H, 2H-5), 4.17-4.21 (m, 1H, H-4), 4.31 (s, 1H, H-3), 4.52 (d, 1H, H-2, $^3J_{1\text{-}2}$ = 3.7 Hz), 6.00 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.7 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 26.2 (C(*C*H$_3$)$_2$), 26.7 (C(*C*H$_3$)$_2$), 60.6 (C-5), 76.7 (C-3), 79.0 (C-4), 85.4 (C-2), 104.9 (C-1), 111.6 (*C*(CH$_3$)$_2$).

Procedure for the synthesis of 1,2-di-*O*-isopropylidene-5-*O*-tosyl-α-D-xylofuranose (**23c**)[149]

Diprotected α-D-xylose **23b** (1.50 g, 7.9 mmol) is dissolved in pyridine (3.73 g, 47.2 mmol) and cooled to 0 °C. To this solution is added dropwise tosyl chloride (1.53 g, 8.0 mmol) in dichloromethane (6 mL) via dropping funnel. After complete addition, the reaction mixture is warmed to room temperature and stirred for further 16 h. After this time, water is added and the layer is

extracted with dichloromethane (3×3 mL). The combined organic phases are washed with aqueous HCl (0.1 M, 3 mL) and dried with over Na_2SO_4. Evaporation under reduced pressure yields a residue, which consists of mono- and ditosylated product. The crude is dissolved in a small amount of dichloromethane, petroleum ether is added and the solution is kept at -20 °C for 2 h. The precipitated product **23c** could be separated by filtration to yield a white solid (1.63 g, 60 %).

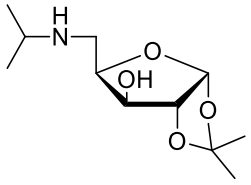


^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.31 (s, 3H, $C(CH_3)_2$), 1.46 (s, 3H, $C(CH_3)_2$), 2.47 (s, 3H, CH_3), 4.10-4.19 (m, 1H, H-3), 4.27-4.35 (m, 3H, H-4 and 2H-5), 4.52 (d, 1H, H-2, $^3J_{1\text{-}2}$ = 3.5 Hz), 5.87 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.5 Hz), 7.33-7.82 (m, 4H, CH-Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 21.5 (CH_3), 26.2 ($C(CH_3)_2$), 26.7 ($C(CH_3)_2$), 66.6 (C-5), 74.4 (C-3), 77.5 (C-4), 84.9 (C-2), 104.9 (C-1), 111.8 ($C(CH_3)_2$), 128.0 ($2CH_{Ar}$), 130.0 ($2CH_{Ar}$), 132.1 (C_{Ar}), 145.2 (C_{Ar}).

Procedure for the synthesis of 5-deoxy-5-*N*-isopropylamino-1,2-*O*-isopropylidene-α-D-xylofuranose (**24b**)[150]

1,2-Di-*O*-isopropylidene-5-*O*-tosyl-α-D-xylofuranose **23c** (3.45 g, 10.0 mmol) and isopropylamine (20 mL) are stirred in a pressure tube at 60 °C for 24 h. The reaction mixture is cooled to room temperature and concentrated *in vacuo*. The residue is taken up in dichloromethane (50 mL), washed with saturated $NaHCO_3$-solution, water and finally with brine (each 20 mL). The organic phase is dried over Na_2SO_4, concentrated *in vacuo* to give **24b** as a yellowish solid (1,42 g, 61 %) after column chromatography ($EtOAc/Et_3N$ = 97:3).



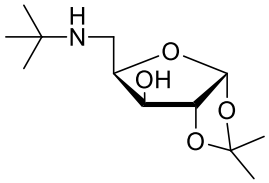
^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) = 1.07 (d, 6H, $CH(CH_3)_2$, $^3J_{H\text{-}H}$ = 6.3 Hz), 1.32 (s, 3H, $C(CH_3)_2$), 1.48 (s, 3H, $C(CH_3)_2$), 2.77 (m, 1H, $CH(CH_3)_2$), 2.97 (dd, 1H, H_A-5, $^2J_{5A\text{-}5B}$ = 12.8 Hz, $^3J_{4\text{-}5A}$ = 1.2 Hz), 3.38 (dd, 1H, H_B-5, $^2J_{5A\text{-}5B}$ = 12.8 Hz, $^3J_{4\text{-}5B}$ = 3.5 Hz), 4.20-4.23 (m, 1H, H-4), 4.28 (d, 1H, H-3, *J* = 2.9 Hz), 4.48 (d, 1H, H-2, $^3J_{1\text{-}2}$ = 3.7 Hz), 5.95 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.7 Hz).

^{13}C NMR (63 MHz, $CDCl_3$): δ (ppm) = 22.3 ($CH(CH_3)_2$), 22.6 ($CH(CH_3)_2$), 26.1 ($C(CH_3)_2$), 26.8 ($C(CH_3)_2$), 46.8 (C-5), 48.6 ($CH(CH_3)_2$), 76.9 (C-3), 78.2 (C-4), 86.1 (C-2), 105.1 (C-1), 111.3 ($C(CH_3)_2$).

General procedure for the synthesis of 5-*N*-alkylamino-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose **24c-g**

1.0 Eq of 1,2-di-*O*-isopropylidene-5-*O*-tosyl-α-D-xylofuranose **23c** and the corresponding amine (4.0 eq) are dissolved in isopropanol (2 mL/1.0 mmol substrate). The mixture is heated to reflux and stirred for 24 h. After cooling to room temperature, it is concentratetd *in vacuo*. The residue is treated with saturated $NaHCO_3$-solution and extracted with diethyl ether (three times). The combined organic phases are dried with Na_2SO_4 and concentrated *in vacuo* to give **24c-g** after column chromatography ($EtOAc/Et_3N$ = 9:1).

5-*N*-*tert*-Butylamino-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose (**24c**)[150]

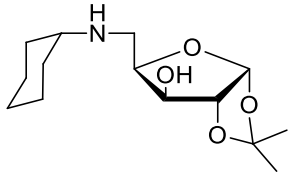


Starting from *tert*-butylamine (4.39 g, 60.0 mmol) and 1,2-di-*O*-isopropylidene-5-*O*-tosyl-α-D-xylofuranose **23c** (5.17 g, 15.0 mmol) in isopropanol (30 mL), the product **24c** was isolated as an off-white solid (1.52 g, 41 %).

^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) = 1.10 (s, 9H, C(CH_3)$_3$), 1.31 (s, 3H, C(CH_3)$_2$), 1.47 (s, 3H, C(CH_3)$_2$), 2.95 (dd, 1H, H_A-5, $^2J_{5A\text{-}5B}$ = 12.7 Hz, $^3J_{4\text{-}5A}$ = 1.2 Hz), 3.35 (dd, 1H, H_B-5, $^2J_{5A\text{-}5B}$ = 12.7 Hz, $^3J_{4\text{-}5B}$ = 3.5 Hz), 4.21-4.24 (m, 1H, H-4), 4.27 (d, 1H, H-3, *J* = 2.9 Hz), 4.46 (d, 1H, H-2, $^3J_{1\text{-}2}$ = 3.7 Hz), 5.94 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.7 Hz).

^{13}C NMR (63 MHz, $CDCl_3$): δ (ppm) = 26.2 (C(*C*H_3)$_2$), 26.9 (C(*C*H_3)$_2$), 28.4 (C(*C*H_3)$_3$), 41.4 (C-5), 50.2 (*C*(CH_3)$_3$), 76.9 (C-3), 78.3 (C-4), 86.1 (C-2), 105.1 (C-1), 111.4 (*C*(CH_3)$_2$).

5-Deoxy-5-*N*-cyclohexylamino-1,2-*O*-isopropylidene-α-D-xylofuranose (**24d**)[150]

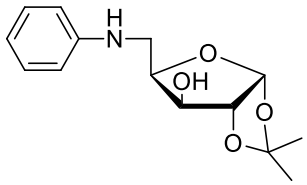


Starting from cyclohexylamine (4.00 g, 40.0 mmol) and 1,2-di-*O*-isopropylidene-5-*O*-tosyl-α-D-xylofuranose **23c** (3.45 g, 10.0 mmol) in isopropanol (20 mL), the product **24d** was isolated as an off-white solid (1.70 g, 63 %).

^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) = 0.98-1.29 (m, 5H, CH_2), 1.31 (s, 3H, C(CH_3)$_2$), 1.47 (s, 3H, C(CH_3)$_2$), 1.55-1.61 (m, 1H, CH_2), 1.68-1.74 (m, 2H, CH_2), 1.82-1.92 (m, 2H, CH_2), 2.35-2.46 (m, 1H, C*H*(CH_2)$_2$, 3.00 (dd, 1H, H_A-5, $^2J_{5A\text{-}5B}$ = 12.9 Hz, $^3J_{4\text{-}5A}$ = 1.3 Hz), 3.46 (dd, 1H, H_B-5, $^2J_{5A\text{-}5B}$ = 12.9 Hz, $^3J_{4\text{-}5B}$ = 3.5 Hz), 4.19-4.22 (m, 1H, H-4), 4.27 (d, 1H, H-3, *J* = 2.9 Hz), 4.48 (d, 1H, H-2, $^3J_{1\text{-}2}$ = 3.7 Hz), 5.95 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.7 Hz).

^{13}C NMR (63 MHz, $CDCl_3$): δ (ppm) = 24.7, 24.7, 25.9 (CH_2), 26.2 (C(*C*H_3)$_2$), 26.8 (C(*C*H_3)$_2$), 32.8, 33.1 (CH_2), 45.5 (C-5), 56.3 (*C*H(CH_2)$_2$), 77.0 (C-3), 78.3 (C-4), 86.1 (C-2), 105.1 (C-1), 111.4 (*C*(CH_3)$_2$).

5-Deoxy-5-*N*-phenylamino-1,2-*O*-isopropylidene-α-D-xylofuranose (**24e**)[112c]

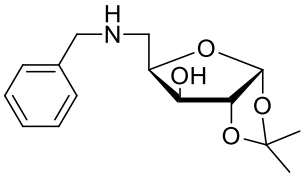


Starting from aniline (3.73 g, 40.0 mmol) and 1,2-di-*O*-isopropylidene-5-*O*-tosyl-α-D-xylofuranose **23c** (3.45 g, 10.0 mmol) in isopropanol (20 mL), the product **24e** was isolated as an off-white solid (2.27 g, 86 %).

^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) = 1.34 (s, 3H, C(CH_3)$_2$), 1.50 (s, 3H, C(CH_3)$_2$), 3.61 (d, 2H, 2H-5, $^3J_{4\text{-}5}$ = 4.0 Hz), 3.90 (s, 1H, NH), 4.32 (d, 1H, H-3, *J* = 2.8 Hz), 4.38-4.43 (m, 1H, H-4), 4.55 (d, 1H, H-2, $^3J_{1\text{-}2}$ = 3.7 Hz), 6.02 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.7 Hz), 6.79-6.90 (m, 3H, CH-Ar), 7.20-7.26 (m, 2H, CH-Ar).

^{13}C NMR (63 MHz, $CDCl_3$): δ (ppm) = 26.1 (C(*C*H_3)), 26.8 (C(*C*H_3)$_2$), 44.0 (C-5), 77.1 (C-3), 77.3 (C-4), 85.6 (C-2), 104.9 (C-1), 111.8 (*C*(CH_3)$_2$), 115.4 (CH_{Ar}), 120.2 (CH_{Ar}), 129.3 (CH_{Ar}), 146.7 (C_{Ar}).

5-Deoxy-5-*N*-benzylamino-1,2-*O*-isopropylidene-α-D-xylofuranose **24f**[150]

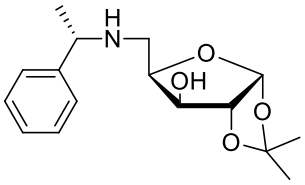


Starting from benzylamine (4.29 g, 40.0 mmol) and 1,2-di-*O*-isopropylidene-5-*O*-tosyl-α-D-xylofuranose **23c** (3.45 g, 10.0 mmol) in isopropanol (20 mL), the product **24f** was isolated as an off-white solid (1.70 g, 61 %).

^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) = 1.32 (s, 3H, $C(CH_3)_2$), 1.47 (s, 3H, $C(CH_3)_2$), 3.00 (dd, 1H, H_A-5, $^2J_{5A\text{-}5B}$ = 13.0 Hz, $^3J_{4\text{-}5A}$ = 1.4 Hz), 3.40 (dd, 1H, H_B-5, $^2J_{5A\text{-}5B}$ = 12.9 Hz, $^3J_{4\text{-}5B}$ = 3.6 Hz), 3.78 (d, 2H, CH_2, *J* = 3.2 Hz), 4.21-4.23 (m, 1H, H-4), 4.29 (d, 1H, H-3, *J* = 2.2 Hz), 4.50 (d, 1H, H-2, $^3J_{1\text{-}2}$ = 3.6 Hz), 5.95 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.6 Hz) 7.26-7.37 (m, 5H, CH-Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 26.3 ($C(CH_3)$), 27.0 ($C(CH_3)_2$), 48.1 (C-5), 54.0 (CH_2), 77.3 (C-3), 78.5 (C-4), 86.3 (C-2), 105.5 (C-1), 111.9 ($C(CH_3)_2$), 128.0 (CH_{Ar}), 128.7 (CH_{Ar}), 129.1 (CH_{Ar}), 139.0 (C_{Ar}).

5-Deoxy-5-*N*-(*S*)-α-methybenzylamino-1,2-*O*-isopropylidene-α-D-xylofuranose (**24g**)



Starting from (*S*)-(–)-α-methylbenzylamine (4.85 g, 40.0 mmol) and 1,2-di-*O*-isopropylidene-5-*O*-tosyl-α-D-xylofuranose **23c** (3.45 g, 10.0 mmol) in isopropanol (20 mL), the product **24g** was isolated as a yellowish, viscous oil (2.90 g, 99 %).

$[\alpha]_D^{26}$ = +5.0 (*c* 1.26, $CHCl_3$).

Anal. calcd for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.90; N, 4.77. Found: C, 65.20; H, 8.01; N, 4.95 %.

HRMS (ESI) calculated for $C_{16}H_{24}NO_4$ 294.16998, found 294.16984.

HRMS (ESI) calculated for $C_{16}H_{23}NO_4Na$ 316.15193, found 316.15178.

^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) = 1.32 (s, 3H, $C(CH_3)_2$), 1.39 (dd, 3H, $CHCH_3$, $^3J_{H\text{-}H}$ = 6.7 Hz), 1.46 (s, 3H, $C(CH_3)_2$), 2.90 (dd, 1H, H_A-5, $^2J_{5A\text{-}5B}$ = 12.9 Hz, $^3J_{4\text{-}5A}$ = 1.4 Hz), 3.18 (dd, 1H, H_B-5, $^2J_{5A\text{-}5B}$ = 12.9 Hz, $^3J_{4\text{-}5B}$ = 3.8 Hz), 3.72 (q, 1H, $CHCH_3$, $^3J_{H\text{-}H}$ = 6.7 Hz), 4.17-4.20 (m, 1H, H-4), 4.30 (d, 1H, H-3, *J* = 2.9 Hz), 4.51 (d, 1H, H-2, $^3J_{1\text{-}2}$ = 3.7 Hz), 5.95 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.7 Hz), 7.20-7.38 (m, 29H, CH-Ar).

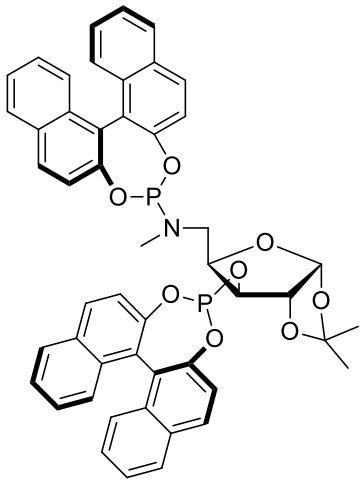
^{13}C NMR (63 MHz, $CDCl_3$): δ (ppm) = 23.2 ($CH(CH_3)$), 26.1 ($C(CH_3)_2$), 26.8 ($C(CH_3)_2$), 46.3 (C-5), 58.1 ($CHCH_3$), 76.9 (C-3), 77.2 (C-4), 85.9 (C-2), 105.0 (C-1), 111.4 ($C(CH_3)_2$), 126.1 (CH_{Ar}), 127.4 (CH_{Ar}), 128.7 (CH_{Ar}), 143.7 (C_{Ar}).

General procedure for the synthesis of amino xylose-based diphosphites **25a-g** and **26b,d-g**

2.2 Eq of enantiopure BINOL are suspended in phosphorus trichloride (1.5 mL/1.0 mmol BINOL), 2-3 drops of *N*-methyl-2-pyrrolidone are added and the solution is heated to 75 °C for 5 min. The resulting HCl gas is derived from the reaction vessel by using a bubble counter (slight argon stream!). The now clear solution is cooled to room temperature, concentrated and dried azeotropically with toluene (three times). Thus, the *in situ* prepared chlorophosphite is dissolved in toluene (8 mL/2.2 mmol BINOL) and triethylamine is added (5 mmol/2.2 mmol BINOL). 1.0 Eq of azeotropically dried amino sugar **24b-g** is dissolved in toluene (8 mL/1.0 mmol substrate) and triethylamine (5.0 eq) is added. This solution is added slowly to the chlorophosphite solution at 0 °C over 5 min and the mixture is kept at this temperature for 5 min. The reaction solution is then stirred at 50 °C for 16 h. After this time, the

mixture is cooled to room temperature and concentrated *in vacuo*. The residue is purified by column chromatography (basic silica, toluene) to give **25a-g** and **26b,d-g**, respectively.

3,5-Bis-(*S*)-[(1,1'-binaphthyl-2,2'-diyl)phosphite]-5-deoxy-5-*N*-methylamino-1,2-*O*-isopropylidene-α-D-xylofuranose (**25a**)



Starting from (*S*)-BINOL (630 mg, 2.2 mmol), 5-Deoxy-5-*N*-methylamino-1,2-*O*-isopropylidene-α-D-xylofuranose (203 mg, 1.0 mmol) and Et_3N (1.01 g, 10.0 mmol) in toluene (16 mL), the product **25a** was isolated as a white solid (703 mg, 85 %, R_f 0.23).

$[\alpha]_D^{26}$ = +335.0 (*c* 0.53, $CHCl_3$).

Anal. calcd for $C_{49}H_{39}NO_8P_2$: C, 70.75; H, 4.73; N, 1.68. Found: C, 69.89; H, 5.00; N, 1.55 %.

HRMS (ESI) calculated for $C_{49}H_{40}NO_8P_2$ 832.22237, found 832.22174.

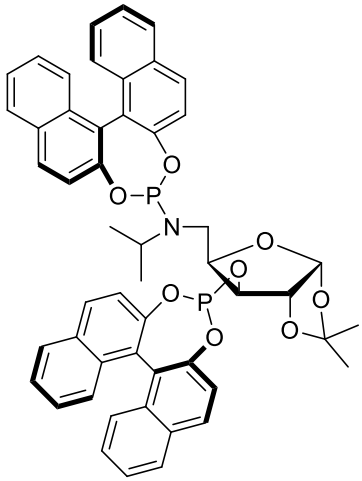
HRMS (ESI) calculated for $C_{49}H_{39}NO_8P_2Na$ 854.20431, found 854.20402.

$^{31}P\{^1H\}$ NMR (101 MHz, C_6D_6): δ (ppm) = 146.1 (d, $J_{P\text{-}P}$ = 4.0 Hz), 154.3 (d, $J_{P\text{-}P}$ = 4.0 Hz).

^1H NMR (250 MHz, C_6D_6): δ (ppm) = 0.97 (s, 3H, $C(CH_3)_2$), 1.36 (s, 3H, $C(CH_3)_2$), 2.48 (d, 3H, CH_3, $^3J_{H\text{-}P}$ = 5.5 Hz), 3.41 (ddd, 1H, H_A-5, $^2J_{5A\text{-}5B}$ = 19.2 Hz, *J* = 14.7 Hz, *J* = 8.1 Hz), 3.82 (ddd, 1H, H_B-5, *J* = 9.9 Hz, *J* = 3.5 Hz), 4.31 (d, 1H, H-2, $^3J_{1\text{-}2}$ = 3.7 Hz), 4.43-4.49 (m, 1H, H-4), 4.64 (dd, 1H, H-3, $^3J_{3\text{-}P}$ = 9.3 Hz, *J* = 2.6 Hz), 5.76 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.7 Hz), 6.83-7.74 (m, 24H, CH-Ar).

^{13}C NMR (75 MHz, C_6D_6): δ (ppm) = 26.2 ($C(CH_3)_2$), 26.9 ($C(CH_3)_2$), 33.9 (d, CH_3, $J_{C\text{-}P}$ = 3.9 Hz), 49.5 (d, C-5, $J_{5\text{-}P}$ = 36.2 Hz), 78.4 (d, C-3, $J_{3\text{-}P}$ = 5.9 Hz), 80.8 (m, C-4), 84.7 (C-2), 105.5 (C-1), 111.8 ($C(CH_3)_2$), 121.9 (CH_{Ar}), 122.1 (d, CH_{Ar}, $J_{C\text{-}P}$ = 1.1 Hz), 122.5 (d, CH_{Ar}, $J_{C\text{-}P}$ = 1.1 Hz), 122.7 (CH_{Ar}), 123.2 (d, C_{Ar}, $J_{C\text{-}P}$ = 2.5 Hz), 123.5 (d, C_{Ar}, $J_{C\text{-}P}$ = 2.5 Hz), 124.7 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.8 Hz), 124.8 (d, C_{Ar}, $J_{C\text{-}P}$ = 2.3 Hz), 124.9 (CH_{Ar}), 125.0 (CH_{Ar}), 125.3 (CH_{Ar}), 125.5 (CH_{Ar}), 126.5 (CH_{Ar}), 126.6 (CH_{Ar}), 126.8 ($2CH_{Ar}$), 127.3 (CH_{Ar}), 127.3 (CH_{Ar}), 127.4 (CH_{Ar}), 127.5 (CH_{Ar}), 128.7 (CH_{Ar}), 128.7 ($3CH_{Ar}$), 130.6 (CH_{Ar}), 130.7 ($2CH_{Ar}$), 131.0 (CH_{Ar}), 131.4 (C_{Ar}), 131.6 (C_{Ar}), 132.0 (C_{Ar}), 132.1 (C_{Ar}), 133.1 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.1 Hz), 133.3 (C_{Ar}), 133.4 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.4 Hz), 133.5 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.4 Hz), 147.7 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 2.3 Hz), 148.8 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 6.1 Hz), 150.2 (C_{Ar}-O) 150.8 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 4.5 Hz).

3,5-Bis-(*S*)-[(1,1'-binaphthyl-2,2'-diyl)phosphite]-5-deoxy-5-*N*-isopropylamino-1,2-*O*-isopropylidene-α-D-xylofuranose (**25b**)



Starting from (*S*)-BINOL (630 mg, 2.2 mmol), 5-Deoxy-5-*N*-isopropylamino-1,2-*O*-isopropylidene-α-D-xylofuranose **24b** (231 mg, 1.0 mmol) and Et_3N (1.01 g, 10.0 mmol) in toluene (16 mL), the product **25b** was isolated as a white solid (653 mg, 76 %, R_f 0.45).

$[\alpha]_D^{25}$ = +427.9 (*c* 0.58, $CHCl_3$).

Anal. calcd for $C_{51}H_{43}NO_8P_2$: C, 71.24; H, 5.04; N, 1.63. Found: C, 71.17; H, 5.36; N, 1.14 %.

HRMS (ESI) calculated for $C_{51}H_{44}NO_8P_2$ 860.25367, found 860.25257.

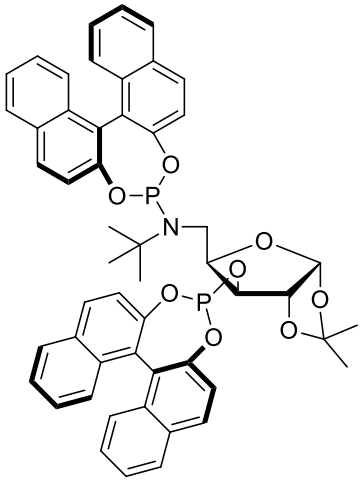
HRMS (ESI) calculated for $C_{51}H_{43}NO_8P_2Na$ 882.23561, found 882.23446.

$^{31}P\{^1H\}$ NMR (101 MHz, C_6D_6): δ (ppm) = 153.3 (d, J_{P-P} = 5.0 Hz), 154.1 (d, J_{P-P} = 5.0 Hz).

^1H NMR (250 MHz, C_6D_6): δ (ppm) = 0.80 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.32 (d, 3H, $CH(CH_3)_2$, $^3J_{H-H}$ = 6.8 Hz), 1.33 (d, 3H, $CH(CH_3)_2$, $^3J_{H-H}$ = 6.8 Hz), 3.27 (ddd, 1H, H_A-5, $^2J_{5A-5B}$ = 15.5 Hz, *J* = 9.4 Hz, *J* = 6.3 Hz), 3.70 (ddd, 1H, H_B-5, $^2J_{5A-5B}$ = 15.5 Hz, *J* = 6.1 Hz, *J* = 3.5 Hz), 3.85 (m, 1H, $CH(CH_3)_2$), 4.08 (d, 1H, H-2, $^3J_{1-2}$ = 3.7 Hz), 4.49-4.57 (m, 2H, H-3 and H-4), 5.57 (d, 1H, H-1, $^3J_{1-2}$ = 3.7 Hz), 6.80-7.76 (m, 24H, CH-Ar).

^{13}C NMR (63 MHz, C_6D_6): δ = 23.0 (d, $CH(CH_3)_2$, J_{C-P} = 9.6 Hz), 23.6 (d, $CH(CH_3)_2$, J_{C-P} = 7.0 Hz), 26.1 ($C(CH_3)_2$), 26.8 ($C(CH_3)_2$), 43.1 (d, C-5, J_{5-P} = 8.1 Hz), 49.3 (d, $CH(CH_3)_2$, J_{C-P} = 25.9 Hz), 78.3 (d, C-3, J_{3-P} = 10.8 Hz), 82.4 (m, C-4), 84.5 (d, C-2, J_{2-P} = 1.5 Hz), 105.2 (C-1), 111.6 ($C(CH_3)_2$), 122.2 (d, CH_{Ar}, J_{C-P} = 1.3 Hz), 122.3 ($2CH_{Ar}$), 122.5 (d, CH_{Ar}, J_{C-P} = 1.4 Hz), 123.0 (d, C_{Ar}, J_{C-P} = 2.2 Hz), 123.4 (d, C_{Ar}, J_{C-P} = 2.5 Hz), 124.7 (d, C_{Ar}, J_{C-P} = 5.2 Hz), 124.8 (CH_{Ar}), 124.9 (d, C_{Ar}, J_{C-P} = 5.2 Hz), 125.0 (CH_{Ar}), 125.2 (CH_{Ar}), 125.4 (CH_{Ar}), 126.5 ($2CH_{Ar}$), 126.7 (CH_{Ar}), 126.7 (CH_{Ar}), 127.3 (CH_{Ar}), 127.4 ($2CH_{Ar}$), 128.5 (CH_{Ar}), 128.6 (CH_{Ar}), 128.7 (CH_{Ar}), 128.7 (CH_{Ar}), 128.8 (CH_{Ar}), 130.0 (CH_{Ar}), 130.7 (CH_{Ar}), 130.8 ($2CH_{Ar}$), 131.4 (C_{Ar}), 131.6 (C_{Ar}), 132.0 (C_{Ar}), 132.0 (C_{Ar}), 133.1 (d, C_{Ar}, J_{C-P} = 1.3 Hz), 133.4 ($2C_{Ar}$), 133.5 (d, C_{Ar}, J_{C-P} = 1.5 Hz), 147.8 (d, C_{Ar}-O, J_{C-P} = 3.1 Hz), 148.5 (d, C_{Ar}-O, J_{C-P} = 5.3 Hz), 150.3 (C_{Ar}-O), 150.8 (d, C_{Ar}-O, J_{C-P} = 4.8 Hz).

3,5-Bis-(*S*)-[(1,1'-binaphthyl-2,2'-diyl)phosphite]-5-deoxy-5-*N*-*tert*-butylamino-1,2-*O*-isopropylidene-α-D-xylofuranose (**25c**)



Starting from (*S*)-BINOL (630 mg, 2.2 mmol), 5-*N*-*tert*-butylamino-5-Deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose **24c** (245 mg, 1.0 mmol) and Et_3N (1.01 g, 10.0 mmol) in toluene (16 mL), the product **25c** was isolated as a white solid (250 mg, 29 %, R_f 0.41).

HRMS (ESI) calculated for $C_{52}H_{46}NO_8P_2$ 874.26932, found 874.26741.

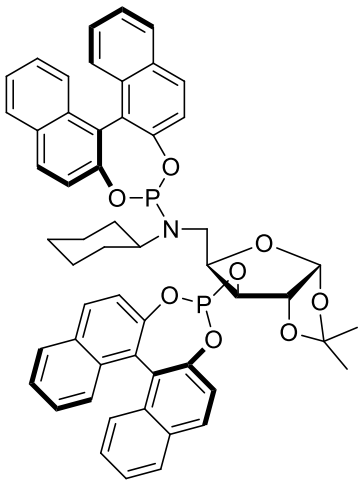
HRMS (ESI) calculated for $C_{52}H_{45}NO_8P_2Na$ 896.25126, found 896.24942.

$^{31}P\{^1H\}$ NMR (101 MHz, C_6D_6): δ (ppm) = 140.8 (s), 143.6 (s).

^1H NMR (250 MHz, C_6D_6): δ (ppm) = 0.70 (s, 3H, $C(CH_3)_2$), 1.31 (s, 3H, $C(CH_3)_2$), 1.62 (d, 9H, $C(CH_3)_3$, $^3J_{H\text{-}P}$ = 2.5 Hz), 3.26 (ddd, 1H, H_A-5, $^2J_{5A\text{-}5B}$ = 16.1 Hz), 3.78 (ddd, 1H, H_B-5, $^2J_{5A\text{-}5B}$ = 16.0 Hz), 3.88 (d, 1H, H-2, $^3J_{1\text{-}2}$ = 3.7 Hz), 4.54-4.57 (m, 2H, H-3 and H-4), 5.43 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.7 Hz), 6.69-7.75 (m, 24H, CH-Ar).

^{13}C NMR (63 MHz, C_6D_6): δ (ppm) = 25.9 ($C(CH_3)_2$), 26.9 ($C(CH_3)_2$), 31.6 (d, $C(CH_3)_3$, $J_{C\text{-}P}$ = 15.8 Hz), 42.7 (d, C-5, $J_{5\text{-}P}$ = 5.8 Hz), 56.2 (d, $C(CH_3)_3$, $J_{C\text{-}P}$ = 22.0 Hz), 78.6 (d, C-3, $J_{3\text{-}P}$ = 12.5 Hz), 84.2 (C-4), 84.3 (C-2), 104.9 (C-1), 111.4 ($C(CH_3)_2$), 122.0 (CH_{Ar}), 122.2 (CH_{Ar}), 122.4 (CH_{Ar}), 122.5 (d, CH_{Ar}, $J_{C\text{-}P}$ = 1.7 Hz), 122.6 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.9 Hz), 123.4 (d, C_{Ar}, $J_{C\text{-}P}$ = 2.7 Hz), 124.6 (d, C_{Ar}, $J_{C\text{-}P}$ = 5.4 Hz), 124.7 (CH_{Ar}), 125.1 ($2CH_{Ar}$), 125.3 (CH_{Ar}), 125.3 (d, C_{Ar}), 126.4 (CH_{Ar}), 126.5 (CH_{Ar}), 126.6 (CH_{Ar}), 126.6 (CH_{Ar}), 127.2 (CH_{Ar}), 127.4 (CH_{Ar}), 127.5 (d, CH_{Ar}, $J_{C\text{-}P}$ = 2.5 Hz), 127.8 (CH_{Ar}), 128.6 ($2CH_{Ar}$), 128.7 (CH_{Ar}), 128.8 (CH_{Ar}), 129.7 (CH_{Ar}), 130.4 (CH_{Ar}) 130.7 (CH_{Ar}), 131.0 (CH_{Ar}), 131.5 (C_{Ar}), 131.6 (C_{Ar}), 132.0 (C_{Ar}), 132.0 (d, C_{Ar}, $J_{C\text{-}P}$ = 0.8 Hz), 133.1 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.5 Hz), 133.4 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.4 Hz), 133.5 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.5 Hz), 133.6 (C_{Ar}), 147.9 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 3.1 Hz), 148.4 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 5.8 Hz), 150.5 (C_{Ar}-O), 151.3 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 5.1 Hz).

3,5-Bis-(*S*)-[(1,1'-binaphthyl-2,2'-diyl)phosphite]-5-deoxy-5-*N*-cyclohexylamino-1,2-*O*-isopropylidene-α-D-xylofuranose (**25d**)



Starting from (*S*)-BINOL (630 mg, 2.2 mmol), 5-Deoxy-5-*N*-cyclohexylamino-1,2-*O*-isopropylidene-α-D-xylofuranose **24d** (272 mg, 1.0 mmol) and Et_3N (1.01 g, 10.0 mmol) in toluene (16 mL), the product **25d** was isolated as a white solid (875 mg, 97 %, R_f 0.50).

$[\alpha]_D^{26}$ = +402.0 (*c* 0.75, $CHCl_3$).

Anal. calcd for $C_{54}H_{47}NO_8P_2$: C, 72.07; H, 5.26; N, 1.56. Found: C, 72.10; H, 5.27; N, 1.39 %.

HRMS (ESI) calculated for $C_{54}H_{48}NO_8P_2$ 900.28497, found 900.28466.

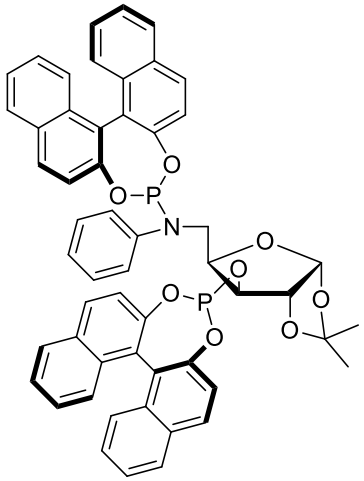
HRMS (ESI) calculated for $C_{54}H_{47}NO_8P_2Na$ 922.26691, found 922.2662.

$^{31}P\{^1H\}$ NMR (101 MHz, C_6D_6): δ (ppm) = 153.6 (d, $J_{P\text{-}P}$ = 3.9 Hz), 155.0 (d, $J_{P\text{-}P}$ = 3.9 Hz).

^{1}H NMR (250 MHz, C_6D_6): δ (ppm) = 0.79 (s, 3H, CH_3), 0.88-1.14 (m, 4H, $2CH_2$), 1.32 (s, 3H, CH_3), 1.55-1.72 (m, 2H, CH_2), 1.77-1.93 (m, 2H, CH_2), 2.11-2.24 (m, 2H, CH_2), 3.24-3.47 (m, 2H, H_A-5 and C*H*$(CH_2)_2$), 3.73 (ddd, 1H, H_B-5, $^{2}J_{5A\text{-}5B}$ = 15.4 Hz, *J* = 6.0 Hz, *J* = 3.5 Hz), 4.07 (d, 1H, H-2, $^{3}J_{1\text{-}2}$ = 3.7 Hz), 4.52-4.58 (m, 2H, H-3 and H-4), 5.58 (d, 1H, H-1, $^{3}J_{1\text{-}2}$ = 3.7 Hz), 6.82-7.79 (m, 24H, CH-Ar).

^{13}C NMR (75 MHz, C_6D_6): δ (ppm) = 25.8 (CH_2), 26.1 (C(*C*$H_3)_2$), 26.7 ($2CH_2$), 26.9 (C(*C*$H_3)_2$), 34.2 (d, CH_2, $J_{C\text{-}P}$ = 9.9 Hz), 35.2 (d, CH_2, $J_{C\text{-}P}$ = 7.8 Hz), 44.1 (d, C-5, $J_{5\text{-}P}$ = 6.1 Hz), 58.6 (d, *C*H$(CH_2)_2$, $J_{C\text{-}P}$ = 23.0 Hz), 78.3 (d, C-3, $J_{3\text{-}P}$ = 10.9 Hz), 82.6 (m, C-4), 84.5 (d, C-2, $J_{2\text{-}P}$ = 1.0 Hz), 105.2 (C-1), 111.6 (*C*$(CH_3)_2$), 122.2 (CH_{Ar}), 122.3 (CH_{Ar}), 122.3 (CH_{Ar}), 122.5 (CH_{Ar}), 123.1 (d, C_{Ar}, $J_{C\text{-}P}$ = 2.0 Hz), 123.4 (d, C_{Ar}, $J_{C\text{-}P}$ = 2.6 Hz), 124.7 (d, C_{Ar}, $J_{C\text{-}P}$ = 5.3 Hz), 124.8 (CH_{Ar}), 125.0 (d, C_{Ar}, $J_{C\text{-}P}$ = 5.3 Hz), 125.0 (CH_{Ar}), 125.2 (CH_{Ar}), 125.3 (CH_{Ar}), 126.5 ($2CH_{Ar}$), 126.7 (CH_{Ar}), 126.7 (CH_{Ar}), 127.3 (CH_{Ar}), 127.4 ($2CH_{Ar}$), 127.6 (CH_{Ar}), 128.6 (CH_{Ar}), 128.7 ($2CH_{Ar}$), 128.8 (CH_{Ar}), 130.0 (CH_{Ar}), 130.7 (CH_{Ar}), 130.8 ($2CH_{Ar}$), 131.4 (C_{Ar}), 131.6 (C_{Ar}), 132.0 (C_{Ar}), 132.0 (C_{Ar}), 133.1 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.1 Hz), 133.4 ($2C_{Ar}$), 133.5 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.4 Hz), 147.8 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 2.9 Hz), 148.6 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 5.6 Hz), 150.5 (C_{Ar}-O), 150.9 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 4.9 Hz).

3,5-Bis-(*S*)-[(1,1'-binaphthyl-2,2'-diyl)phosphite]-5-deoxy-5-*N*-phenylamino-1,2-*O*-isopropylidene-α-D-xylofuranose (**25e**)



Starting from (*S*)-BINOL (630 mg, 2.2 mmol), 5-Deoxy-5-*N*-phenylamino-1,2-*O*-isopropylidene-α-D-xylofuranose **24e** (265 mg, 1.0 mmol) and Et_3N (1.01 g, 10.0 mmol) in toluene (16 mL), the product **25e** was isolated as a white solid (291 mg, 33 %, R_f 0.27).

$[\alpha]_D^{25}$ = +150.9 (*c* 0.53, $CHCl_3$).

Anal. calcd for $C_{54}H_{41}NO_8P_2$: C, 72.56; H, 4.62; N, 1.57. Found: C, 72.23; H, 4.44; N, 1.47 %.

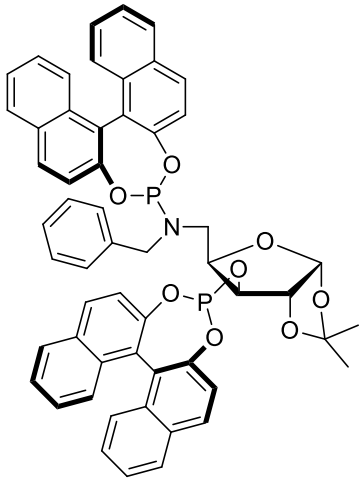
HRMS (EI) calculated for $C_{54}H_{41}NO_8P_2$ 893.23019, found 893.22940.

^{31}P{^{1}H} NMR (101 MHz, C_6D_6): δ (ppm) = 146.3 (s), 150.8 (s).

^{1}H NMR (250 MHz, C_6D_6): δ (ppm) = 0.78 (s, 3H, C$(CH_3)_2$), 1.13 (s, 3H, C$(CH_3)_2$), 3.80 (ddd, 1H, H_A-5, $^{2}J_{5A\text{-}5B}$ = 14.6 Hz, *J* = 5.7 Hz, *J* = 3.2 Hz), 4.06-4.15 (m, 1H, H_B-5), 4.14 (d, 1H, H-2, $^{3}J_{1\text{-}2}$ = 3.6 Hz), 4.43-4.46 (m, 1H, H-4), 4.58 (dd, 1H, H-3, $^{3}J_{3\text{-}P}$ = 8.5 Hz, *J* = 2.5 Hz), 5.46 (d, 1H, H-1, $^{3}J_{1\text{-}2}$ = 3.7 Hz), 6.82-7.73 (m, 29H, CH-Ar).

^{13}C NMR (63 MHz, C_6D_6): δ (ppm) = 26.1 (C(*C*$H_3)_2$), 26.7 (C(*C*$H_3)_2$), 46.7 (C-5), 77.6 (m, C-4), 79.2 (d, C-3, $J_{3\text{-}P}$ = 6.5 Hz), 84.5 (C-2), 104.8 (C-1), 111.6 (*C*$(CH_3)_2$), 122.1 (CH_{Ar}), 122.2 (CH_{Ar}), 122.3 (CH_{Ar}), 122.5 (CH_{Ar}), 122.5 (d, C_{Ar}), 123.1 (d, C_{Ar}, $J_{C\text{-}P}$ = 2.3 Hz), 124.8 (d, C_{Ar}, $J_{C\text{-}P}$ = 5.4Hz), 124.9 (d, C_{Ar}) 125.0 (CH_{Ar}), 125.2 ($3CH_{Ar}$), 125.3 (CH_{Ar}), 126.0 (CH_{Ar}), 126.2 (CH_{Ar}), 126.6 ($3CH_{Ar}$), 126.7 (CH_{Ar}), 127.2 (CH_{Ar}), 127.4 (CH_{Ar}), 127.6 (CH_{Ar}), 128.6 (CH_{Ar}) 128.7 ($2CH_{Ar}$), 128.8 ($2CH_{Ar}$), 129.6 ($2CH_{Ar}$), 130.2 (CH_{Ar}), 130.7 (CH_{Ar}), 130.8 (CH_{Ar}), 131.0 (CH_{Ar}), 131.5 ($2C_{Ar}$), 132.1 (C_{Ar}), 132.1 (C_{Ar}), 133.0 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.3 Hz), 133.3 (d, C_{Ar}, $J_{C\text{-}P}$ = 0.9 Hz), 133.4 (d, C_{Ar}, $J_{C\text{-}P}$ = 2.0 Hz), 133.5 (d, C_{Ar}, $J_{C\text{-}P}$ = 2.0 Hz), 144.1 (d, C_{Ar}, $J_{C\text{-}P}$ = 20.0 Hz), 147.8 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 2.7 Hz), 148.7 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 5.9 Hz), 149.7 (C_{Ar}-O), 150.4 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 5.5 Hz).

3,5-Bis-(*S*)-[(1,1'-binaphthyl-2,2'-diyl)phosphite]-5-deoxy-5-*N*-benzylamino-1,2-*O*-isopropylidene-α-D-xylofuranose (**25f**)



Starting from (*S*)-BINOL (630 mg, 2.2 mmol), 5-Deoxy-5-*N*-benzylamino-1,2-*O*-isopropylidene-α-D-xylofuranose **24f** (279 mg, 1.0 mmol) and Et_3N (1.01 g, 10.0 mmol) in toluene (16 mL), the product **25f** was isolated as a white solid (731 mg, 81 %, R_f 0.60).

$[\alpha]_D^{27}$ = +319.2 (*c* 0.80, $CHCl_3$).

Anal. calcd for $C_{55}H_{43}NO_8P_2$: C, 72.76; H, 4.77; N, 1.54. Found: C, 72.92; H, 4.80; N, 1.50 %.

HRMS (ESI) calculated for $C_{55}H_{44}NO_8P_2$ 908.25367, found 908.25315.

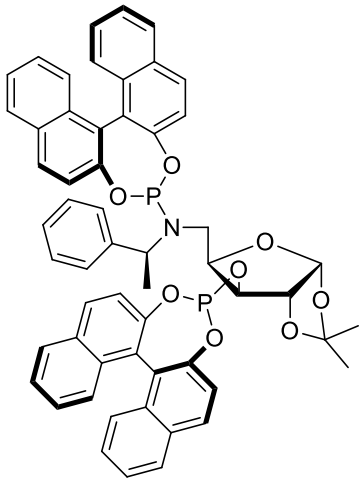
HRMS (ESI) calculated for $C_{55}H_{43}NO_8P_2Na$ 930.23561, found 930.23403.

$^{31}P\{^1H\}$ NMR (101 MHz, C_6D_6): δ (ppm) = 152.2 (s), 152.3 (s).

^1H NMR (250 MHz, C_6D_6): δ (ppm) = 0.93 (s, 3H, $C(CH_3)_2$), 1.40 (s, 3H, $C(CH_3)_2$), 3.39 (ddd, 1H, H_A-5, $^2J_{5A\text{-}5B}$ = 19.3 Hz, *J* = 15.1 Hz, *J* = 8.3 Hz), 3.61 (ddd, 1H, H_B-5, $^2J_{5A\text{-}5B}$ = 15.1 Hz), 4.23 (d, 1H, H-2, $^3J_{1\text{-}2}$ = 3.8 Hz), 4.30 (dd, 1H, H_A-NCH_2, $^2J_{A\text{-}B}$ = 14.9 Hz, $^3J_{A\text{-}P}$ = 10.4 Hz), 4.45 (dd, 1H, H-3, $^3J_{3\text{-}P}$ = 9.4 Hz, *J* = 2.6 Hz), 4.53-4.61 (dd, 1H, H_B-NCH_2, $^2J_{A\text{-}B}$ = 14.9 Hz, $^3J_{B\text{-}P}$ = 6.3 Hz), 4.64-4.69 (m, 1H, H-4), 5.69 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.8 Hz), 6.83-7.74 (m, 29H, CH-Ar).

^{13}C NMR (63 MHz, C_6D_6): δ (ppm) = 26.1 ($C(CH_3)_2$), 26.9 ($C(CH_3)_2$), 45.0 (d, C-5, $J_{5\text{-}P}$ = 23.2 Hz), 50.3 (d, CH_2Ph, $J_{C\text{-}P}$ = 14.1 Hz), 78.9 (d, C-3, $J_{3\text{-}P}$ = 13.6 Hz), 82.9 (m, C-4), 84.4 (d, C-2, $J_{2\text{-}P}$ = 1.3 Hz), 105.7 (C-1), 111.8 ($C(CH_3)_2$), 122.1 ($2CH_{Ar}$), 122.5 ($2CH_{Ar}$), 123.2 (d, C_{Ar}, $J_{C\text{-}P}$ = 2.5 Hz), 123.3 (d, C_{Ar}, $J_{C\text{-}P}$ = 2.0 Hz), 124.8 (d, C_{Ar}, $J_{C\text{-}P}$ = 5.3 Hz), 124.9 (CH_{Ar}), 124.9 (d, C_{Ar}), 125.1 (CH_{Ar}), 125.2 (CH_{Ar}), 125.4 (CH_{Ar}), 126.6 ($2CH_{Ar}$), 126.6 (CH_{Ar}), 126.8 (CH_{Ar}), 127.2 (CH_{Ar}), 127.3 (CH_{Ar}), 127.4 (CH_{Ar}), 127.4 (CH_{Ar}), 127.6 (CH_{Ar}), 128.6 ($3CH_{Ar}$), 128.7 (CH_{Ar}), 128.7 (CH_{Ar}), 128.8 (CH_{Ar}), 129.5 ($2CH_{Ar}$), 130.4 (CH_{Ar}), 130.8 ($2CH_{Ar}$), 131.2 (CH_{Ar}), 131.4 (C_{Ar}), 131.6 (C_{Ar}), 132.0 (C_{Ar}), 132.1 (C_{Ar}), 133.1 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.1 Hz), 133.2 (C_{Ar}), 133.4 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.2 Hz), 133.5 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.3 Hz), 139.1 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.3 Hz), 147.7 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 2.7 Hz), 148.5 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 6.0 Hz), 150.1 (C_{Ar}-O), 150.6 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 4.4 Hz).

3,5-Bis-(*S*)-[(1,1'-binaphthyl-2,2'-diyl)phosphite]-5-deoxy-5-*N*-(*S*)-α-methylbenzylamino-1,2-*O*-isopropylidene-α-D-xylofuranose (**25g**)



Starting from (*S*)-BINOL (630 mg, 2.2 mmol), 5-Deoxy-5-*N*-(*S*)-α-methylbenzylamino-1,2-*O*-isopropylidene-α-D-xylofuranose **24g** (294 mg, 1.0 mmol) and Et_3N (1.01 g, 10.0 mmol) in toluene (16 mL), the product **25g** was isolated as a white solid (824 mg, 89 %, R_f 0.36).

$[\alpha]_D^{23}$ = +313.8 (*c* 1.00, $CHCl_3$).

Anal. calcd for $C_{56}H_{45}NO_8P_2$: C, 72.96; H, 4.92; N, 1.52. Found: C, 72.92; H, 5.88; N, 1.25 %.

HRMS (ESI) calculated for $C_{56}H_{46}NO_8P_2$ 922.26932, found 922.26841.

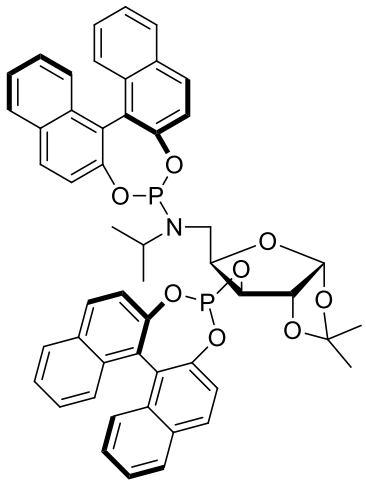
HRMS (ESI) calculated for $C_{56}H_{45}NO_8P_2Na$ 944.25126, found 944.2514.

$^{31}P\{^1H\}$ NMR (121 MHz, C_6D_6): δ (ppm) = 149.7 (s), 156.1 (s).

^1H NMR (300 MHz, C_6D_6): δ (ppm) = 0.76 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 1.80 (dd, 3H, CHCH_3, $^3J_{H\text{-}H}$ = 7.1 Hz, $^3J_{H\text{-}P}$ = 3.8 Hz), 3.02 (ddd, 1H, H_A-5, $^2J_{5A\text{-}5B}$ = 15.2 Hz, *J* = 7.2 Hz, *J* = 2.8 Hz), 3.52 (ddd, 1H, H_B-5, $^2J_{5A\text{-}5B}$ = 15.2 Hz, $^3J_{5B\text{-}P}$ = 2.9 Hz, $^3J_{5A\text{-}H}$ = 2.9 Hz), 3.98 (d, 1H, H-2, $^3J_{1\text{-}2}$ = 3.8 Hz), 4.27 (dd, 1H, H-3, $^3J_{3\text{-}P}$ = 8.9 Hz, *J* = 2.6 Hz), 4.52-4.56 (m, 1H, H-4), 5.06 (dq, 1H, C*H*CH_3, $^3J_{H\text{-}P}$ = 14.2 Hz, $^3J_{H\text{-}H}$ = 7.1 Hz), 5.50 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.8 Hz), 6.80-7.77 (m, 29H, CH-Ar).

^{13}C NMR (75 MHz, C_6D_6): δ (ppm) = 23.2 (d, CH(*C*H_3), $J_{C\text{-}P}$ = 30.4 Hz), 25.9 (C(*C*H_3)$_2$), 26.8 (C(*C*H_3)$_2$), 45.5 (C-5), 59.6 (d, *C*HCH_3, $J_{C\text{-}P}$ = 23.7 Hz), 78.8 (d, C-3, $J_{3\text{-}P}$ = 15.8 Hz), 83.0 (m, C-4), 84.1 (C-2), 105.5 (C-1), 111.5 (*C*(CH$_3$)$_2$), 122.0 (CH_{Ar}), 122.2 (CH_{Ar}), 122.4 (CH_{Ar}), 122.5 (CH_{Ar}), 122.7 (d, C_{Ar}, $J_{C\text{-}P}$ = 2.2 Hz), 123.3 (d, C_{Ar}, $J_{C\text{-}P}$ = 2.5 Hz), 124.7 (d, C_{Ar}), 124.7 (CH_{Ar}), 125.0 (d, C_{Ar}, $J_{C\text{-}P}$ = 5.3 Hz), 125.1 (CH_{Ar}), 125.2 (CH_{Ar}), 125.4 (CH_{Ar}), 126.4 (CH_{Ar}), 126.5 (CH_{Ar}), 126.6 (CH_{Ar}), 126.7 (CH_{Ar}), 127.2 (CH_{Ar}), 127.3 (CH_{Ar}), 127.4 (CH_{Ar}), 127.6 (CH_{Ar}), 127.7 (CH_{Ar}), 128.2 (CH_{Ar}), 128.3 (CH_{Ar}), 128.6 (CH_{Ar}), 128.7 (2CH_{Ar}), 128.9 (3CH_{Ar}), 130.1 (CH_{Ar}) 130.5 (CH_{Ar}), 130.8 (CH_{Ar}), 131.3 (CH_{Ar}), 131.3 (C_{Ar}) 131.5 (C_{Ar}), 132.0 (2C_{Ar}), 133.1 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.3 Hz), 133.3 (C_{Ar}), 133.4 (d, C_{Ar}, $J_{C\text{-}P}$ = 0.9 Hz), 133.5 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.6 Hz), 144.9 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.2 Hz), 147.8 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 3.0 Hz), 148.5 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 5.9 Hz), 150.4 (C_{Ar}-O), 151.0 (d, C_{Ar}-O $J_{C\text{-}P}$ = 5.1 Hz).

3,5-Bis-(*R*)-[(1,1'-binaphthyl-2,2'-diyl)phosphite]-5-deoxy-5-*N*-isopropylamino-1,2-*O*-isopropylidene-α-D-xylofuranose (**26b**)



Starting from (*R*)-BINOL (630 mg, 2.2 mmol), 5-Deoxy-5-*N*-isopropylamino-1,2-*O*-isopropylidene-α-D-xylofuranose **24b** (231 mg, 1.0 mmol) and Et_3N (1.01 g, 10.0 mmol) in toluene (16 mL), the product **26b** was isolated as a white solid (777 mg, 90 %, R_f 0.25).

$[\alpha]_D^{27}$ = -392.0 (*c* 0.71, $CHCl_3$).

Anal. calcd for $C_{51}H_{43}NO_8P_2$: C, 71.24; H, 5.04; N, 1.63. Found: C, 71.16; H, 5.08; N, 1.10 %.

HRMS (ESI) calculated for $C_{51}H_{44}NO_8P_2$ 860.25367, found 860.25359.

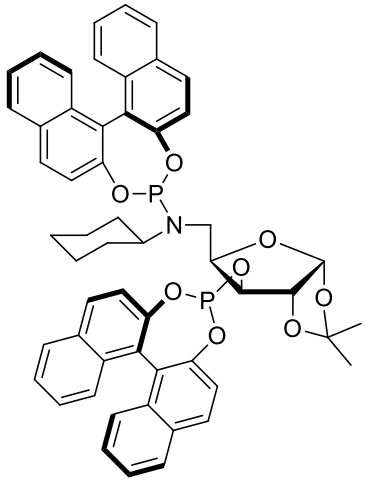
HRMS (ESI) calculated for $C_{51}H_{43}NO_8P_2Na$ 882.23561, found 882.2354.

$^{31}P\{^1H\}$ NMR (121 MHz, C_6D_6): δ (ppm) = 151.4 (d, $J_{P\text{-}P}$ = 8.3 Hz), 153.3 (d, $J_{P\text{-}P}$ = 8.4 Hz).

^1H NMR (300 MHz, C_6D_6): δ (ppm) = 1.05 (s, 3H, CH_3), 1.08 (d, 3H, $CH(CH_3)_2$, $^3J_{H\text{-}H}$ = 6.8 Hz), 1.12 (d, 3H, $CH(CH_3)_2$, $^3J_{H\text{-}H}$ = 6.7 Hz), 1.39 (s, 3H, CH_3), 3.42 (ddd, 1H, H_A-5, $^2J_{5A\text{-}5B}$ = 16.4 Hz, *J* = 10.1 Hz, *J* = 6.9 Hz), 3.68-3.82 (m, 2H, H_B-5 and $CH(CH_3)_2$), 4.43-4.49 (m, 2H, H-3 and H-4), 4.61 (d, 1H, H-2, $^3J_{1\text{-}2}$ = 3.7 Hz), 5.81 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.7 Hz), 6.82-7.80 (m, 24H, CH-Ar).

^{13}C NMR (75 MHz, C_6D_6): δ (ppm) = 22.3 (d, $CH(CH_3)_2$, $J_{C\text{-}P}$ = 6.6 Hz), 23.3 (d, $CH(CH_3)_2$, $J_{C\text{-}P}$ = 5.0 Hz), 26.5 ($C(CH_3)_2$), 27.1 ($C(CH_3)_2$), 42.7 (d, C-5, $J_{5\text{-}P}$ = 20.9 Hz), 48.2 (d, $CH(CH_3)_2$, $J_{C\text{-}P}$ = 15.7 Hz), 79.0 (d, C-3, $J_{3\text{-}P}$ = 11.9 Hz), 81.8 (m, C-4), 85.0 (d, C-2, $J_{2\text{-}P}$ = 3.1 Hz), 105.2 (C-1), 111.9 ($C(CH_3)_2$), 121.8 (CH_{Ar}), 122.1 (CH_{Ar}), 122.6 (CH_{Ar}), 122.8 (CH_{Ar}), 123.3 (d, C_{Ar}, $J_{C\text{-}P}$ = 2.2 Hz), 123.4 (d, C_{Ar}, $J_{C\text{-}P}$ = 2.5 Hz), 124.6 (d, C_{Ar}, $J_{C\text{-}P}$ = 4.6 Hz), 124.7 (d, C_{Ar}, $J_{C\text{-}P}$ = 4.9 Hz), 125.0 (CH_{Ar}), 125.1 (CH_{Ar}), 125.3 (CH_{Ar}), 125.3 (CH_{Ar}), 126.5 (CH_{Ar}), 126.7 ($3CH_{Ar}$), 127.4 ($2CH_{Ar}$), 127.5 ($2CH_{Ar}$), 128.6 (CH_{Ar}), 128.7 (CH_{Ar}), 128.7 (CH_{Ar}), 128.7 (CH_{Ar}), 130.3 (CH_{Ar}), 130.4 (CH_{Ar}), 130.8 ($2CH_{Ar}$), 131.2 (C_{Ar}), 131.6 (C_{Ar}), 132.0 (C_{Ar}), 132.1 (C_{Ar}), 133.2 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.1 Hz), 133.3 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.5 Hz), 133.5 ($2C_{Ar}$), 147.6 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 2.1 Hz), 148.5 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 5.5 Hz), 150.4 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 5.9 Hz), 150.6 (C_{Ar}-O).

3,5-Bis-(*R*)-[(1,1'-binaphthyl-2,2'-diyl)phosphite]-5-deoxy-5-*N*-cyclohexylamino-1,2-*O*-isopropylidene-α-D-xylofuranose (**26d**)



Starting from (*R*)-BINOL (630 mg, 2.2 mmol), 5-Deoxy-5-*N*-cyclohexylamino-1,2-*O*-isopropylidene-α-D-xylofuranose **24d** (272 mg, 1.0 mmol) and Et_3N (1.01 g, 10.0 mmol) in toluene (16 mL), the product **26d** was isolated as a white solid (876 mg, 97 %, R_f 0.33).

$[\alpha]_D^{22}$ = -298.6 (*c* 1.00, $CHCl_3$).

Anal. calcd for $C_{54}H_{47}NO_8P_2$: C, 72.07; H, 5.26; N, 1.56. Found: C, 72.06; H, 5.12; N, 1.49 %.

HRMS (ESI) calculated for $C_{54}H_{48}NO_8P_2$ 900.28497, found 900.28497.

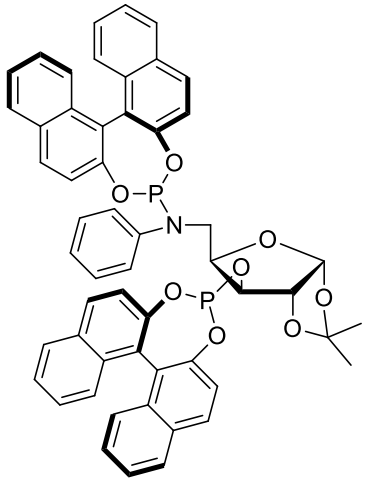
HRMS (ESI) calculated for $C_{54}H_{47}NO_8P_2Na$ 922.26691, found 922.26696.

$^{31}P\{^1H\}$ NMR (101 MHz, C_6D_6): δ (ppm) = 151.9 (d, $J_{P\text{-}P}$ = 10.1 Hz), 155.0 (d, $J_{P\text{-}P}$ = 10.2 Hz).

^1H NMR (250 MHz, C_6D_6): δ (ppm) = 0.73 (m, 3H, 1.5CH_2), 1.05 (s, 3H, CH_3), 1.23-1.36 (m, 2H, CH_2), 1.42 (s, 3H, CH_3), 1.57-1.70 (m, 3H, 1.5CH_2), 1.84-1.95 (m, 2H, CH_2), 3.14-3.27 (m, 1H, C*H*(CH_2)$_2$), 3.38-3.51 (m, 1H, H_A-5), 3.74 (ddd, 1H, H_B-5, $^2J_{5A\text{-}5B}$ = 15.4 Hz, *J* = 12.1 Hz, *J* = 3.3 Hz), 4.51-4.56 (m, 2H, H-3 and H-4), 4.64 (d, 1H, H-2, $^3J_{1\text{-}2}$ = 3.6 Hz), 5.82 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.7 Hz), 6.82-7.79 (m, 24H, CH-Ar).

^{13}C NMR (63 MHz, C_6D_6): δ (ppm) = 25.8 (CH_2), 26.5 (C(*C*H_3)$_2$), 26.6 (CH_2), 26.7 (CH_2), 27.1 (C(*C*H_3)$_2$), 33.9 (d, CH_2, $J_{C\text{-}P}$ = 7.0 Hz), 34.3 (d, CH_2, $J_{C\text{-}P}$ = 6.3 Hz), 43.4 (d, C-5, $J_{5\text{-}P}$ = 22.0 Hz), 57.3 (d, *C*H(CH_2)$_2$, $J_{C\text{-}P}$ = 12.5 Hz), 78.9 (d, C-3, $J_{3\text{-}P}$ = 12.1 Hz), 82.0 (m, C-4), 85.0 (d, C-2, $J_{2\text{-}P}$ = 3.3 Hz), 105.2 (C-1), 111.9 (*C*(CH_3)$_2$), 121.8 (CH_{Ar}), 122.1 (CH_{Ar}), 122.7 (2CH_{Ar}), 123.3 (d, C_{Ar}, $J_{C\text{-}P}$ = 2.2 Hz), 123.4 (d, C_{Ar}, $J_{C\text{-}P}$ = 2.6 Hz), 124.6 (d, C_{Ar}, $J_{C\text{-}P}$ = 5.1 Hz), 124.7 (d, C_{Ar}, $J_{C\text{-}P}$ = 5.5 Hz), 125.0 (CH_{Ar}), 125.0 (CH_{Ar}), 125.3 (CH_{Ar}), 125.3 (CH_{Ar}), 126.5 (CH_{Ar}), 126.7 (3CH_{Ar}), 127.4 (2CH_{Ar}), 127.5 (2CH_{Ar}), 128.4 (CH_{Ar}), 128.7 (CH_{Ar}), 128.7 (2CH_{Ar}), 130.3 (CH_{Ar}), 130.4 (CH_{Ar}), 130.8 (CH_{Ar}), 130.9 (CH_{Ar}), 131.2 (C_{Ar}), 131.6 (C_{Ar}), 131.9 (C_{Ar}), 132.1 (C_{Ar}), 133.2 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.4 Hz), 133.3 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.5 Hz), 133.5 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.0 Hz), 133.5 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.6 Hz), 147.7 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 2.0 Hz), 148.5 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 5.3 Hz), 150.5 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 5.5 Hz), 150.6 (C_{Ar}-O).

3,5-Bis-(*R*)-[(1,1'-binaphthyl-2,2'-diyl)phosphite]-5-deoxy-5-*N*-phenylamino-1,2-*O*-isopropylidene-α-D-xylofuranose (**26e**)



Starting from (*R*)-BINOL (630 mg, 2.2 mmol), 5-Deoxy-5-*N*-phenylamino-1,2-*O*-isopropylidene-α-D-xylofuranose **24e** (265 mg, 1.0 mmol) and Et_3N (1.01 g, 10.0 mmol) in toluene (16 mL), the product **26e** was isolated as a white solid (291 mg, 33 %, R_f 0.18).

$[\alpha]_D^{26}$ = -265.2 (*c* 0.50, $CHCl_3$).

Anal. calcd for $C_{54}H_{41}NO_8P_2$: C, 72.56; H, 4.62; N, 1.57. Found: C, 72.25; H, 4.51; N, 1.66 %.

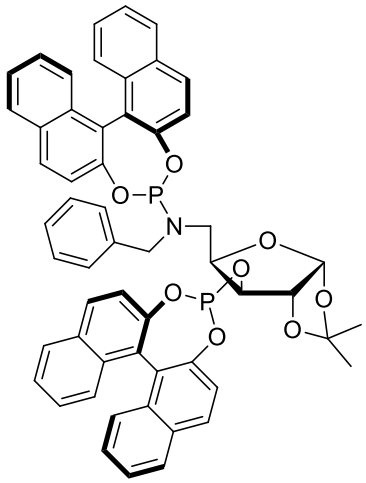
HRMS (EI) calculated for $C_{54}H_{41}NO_8P_2$ 893.23019, found 893.23177.

$^{31}P\{^1H\}$ NMR (101 MHz, C_6D_6): δ (ppm) = 146.9 (d, $J_{P\text{-}P}$ = 8.9 Hz), 147.7 (d, $J_{P\text{-}P}$ = 9.0 Hz).

^1H NMR (250 MHz, C_6D_6): δ (ppm) = 0.89 (s, 3H, $C(CH_3)_2$), 1.09 (s, 3H, $C(CH_3)_2$), 3.87-4.11 (m, 2H, 2H-5), 4.33-4.39 (m, 1H, H-4), 4.45 (dd, 1H, H-3, $^3J_{3\text{-}P}$ = 9.6 Hz, J = 2.7 Hz), 4.55 (d, 1H, H-2, $^3J_{1\text{-}2}$ = 3.6 Hz), 5.69 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.6 Hz), 6.82-7.70 (m, 29H, CH-Ar).

^{13}C NMR (63 MHz, C_6D_6): δ (ppm) = 26.4 ($C(CH_3)_2$), 26.8 ($C(CH_3)_2$), 47.4 (d, C-5, $J_{5\text{-}P}$ = 16.1 Hz), 78.5 (m, C-4), 78.8 (d, C-3, $J_{3\text{-}P}$ = 8.5 Hz), 84.9 (d, C-2, $J_{2\text{-}P}$ = 2.6 Hz), 104.9 (C-1), 112.0 ($C(CH_3)_2$), 121.6 (CH_{Ar}), 122.2 (CH_{Ar}), 122.4 (CH_{Ar}), 122.5 (CH_{Ar}), 123.3 (d, C_{Ar}, $J_{C\text{-}P}$ = 2.3 Hz), 123.3 (d, C_{Ar}, $J_{C\text{-}P}$ = 2.3 Hz), 124.7 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.2 Hz C_{Ar}), 124.8 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.0 Hz), 125.0 (CH_{Ar}), 125.1 (CH_{Ar}), 125.3 (CH_{Ar}), 125.4 (CH_{Ar}), 125.8 (CH_{Ar}), 126.5 (CH_{Ar}), 126.6 (CH_{Ar}), 126.8 (CH_{Ar}), 126.8 (CH_{Ar}), 127.4 ($3CH_{Ar}$), 127.5 (CH_{Ar}), 128.0 (CH_{Ar}), 128.1 (CH_{Ar}), 128.6 (CH_{Ar}), 128.7 (CH_{Ar}), 128.7 ($2CH_{Ar}$), 129.4 ($2CH_{Ar}$), 130.4 ($2CH_{Ar}$), 130.8 (CH_{Ar}), 130.9 (CH_{Ar}), 131.2 (C_{Ar}), 131.5 (C_{Ar}), 132.0 (C_{Ar}), 132.1 (C_{Ar}), 133.2 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.0 Hz), 133.3 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.2 Hz), 133.3 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.6 Hz), 133.5 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.4 Hz), 143.2 (d, C_{Ar}, $J_{C\text{-}P}$ = 12.5 Hz), 147.7 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 1.8 Hz), 148.7 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 5.3 Hz), 149.9 (C_{Ar}-O), 150.3 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 5.6 Hz).

3,5-Bis-(*R*)-[(1,1'-binaphthyl-2,2'-diyl)phosphite]-5-deoxy-5-*N*-benzylamino-1,2-*O*-isopropylidene-α-D-xylofuranose (**26f**)



Starting from (*R*)-BINOL (630 mg, 2.2 mmol), 5-Deoxy-5-*N*-benzylamino-1,2-*O*-isopropylidene-α-D-xylofuranose **24f** (279 mg, 1.0 mmol) and Et_3N (1.01 g, 10.0 mmol) in toluene (16 mL), the product **26f** was isolated as a white solid (770 mg, 85 %, R_f 0.23).

$[\alpha]_D^{25}$ = -263.1 (*c* 0.31, $CHCl_3$).

Anal. calcd for $C_{55}H_{43}NO_8P_2$: C, 72.76; H, 4.77; N, 1.54. Found: C, 72.85; H, 4.88; N, 1.45 %.

HRMS (ESI) calculated for $C_{55}H_{44}NO_8P_2$ 908.25367, found 908.25397.

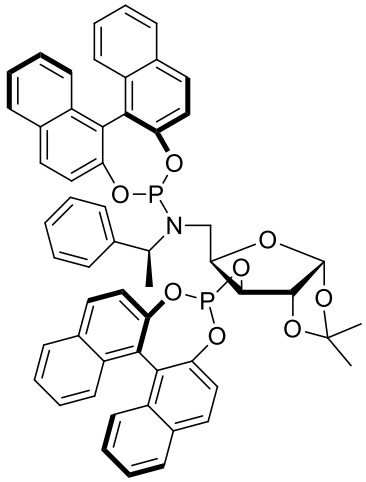
HRMS (ESI) calculated for $C_{55}H_{43}NO_8P_2Na$ 930.23561, found 930.23455.

$^{31}P\{^1H\}$ NMR (101 MHz, C_6D_6): δ (ppm) = 143.6 (d, $J_{P\text{-}P}$ = 5.0 Hz), 150.9 (d, $J_{P\text{-}P}$ = 5.0 Hz).

^{1}H NMR (250 MHz, C_6D_6): δ (ppm) = 1.00 (s, 3H, C(CH_3)$_2$), 1.37 (s, 3H, C(CH_3)$_2$), 3.42 (ddd, 1H, H_A-5, $^{2}J_{5A\text{-}5B}$ = 15.1 Hz, J = 2.2 Hz), 3.67 (dd, 1H, H_A-NCH_2, $^{2}J_{A\text{-}B}$ = 15.4 Hz, J = 4.5 Hz), 3.78-3.92 (m, 1H, H_B-5), 4.37 (dd, 1H, H-3, $^{3}J_{3\text{-}P}$ = 10.2 Hz, J = 2.6 Hz), 4.53-4.61 (m, 2H, H_B-NCH_2 and H-4), 4.63 (d, 1H, H-2, $^{3}J_{1\text{-}2}$ = 3.7 Hz), 5.87 (d, 1H, H-1, $^{3}J_{1\text{-}2}$ = 3.6 Hz), 6.81-7.70 (m, 27H, CH-Ar), 7.84 (m, 1H, CH-Ar), 8.05 (m, 1H, CH-Ar).

^{13}C NMR (75 MHz, C_6D_6): δ (ppm) = 26.3 (C(CH_3)$_2$), 27.1 (C(CH_3)$_2$), 45.6 (d, C-5, $J_{5\text{-}P}$ = 36.5 Hz), 48.0 (CH_2Ph), 76.3 (m, C-4), 79.1 (d, C-3, $J_{3\text{-}P}$ = 2.4 Hz), 85.4 (d, C-2, $J_{2\text{-}P}$ = 1.9 Hz), 105.2 (C-1), 111.8 (C(CH_3)$_2$), 121.5 (CH_{Ar}), 122.0 (CH_{Ar}), 122.6 (CH_{Ar}), 123.0 (CH_{Ar}), 123.0 (d, C_{Ar}, $J_{C\text{-}P}$ = 2.4 Hz), 123.9 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.9 Hz), 124.6 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.1 Hz), 124.7 (C_{Ar}), 125.0 (CH_{Ar}), 125.0 (CH_{Ar}), 125.3 (CH_{Ar}), 125.4 (CH_{Ar}), 126.4 (CH_{Ar}), 126.5 (CH_{Ar}), 126.7 (CH_{Ar}), 126.8 (CH_{Ar}), 127.3 (CH_{Ar}), 127.4 (3CH_{Ar}), 127.5 (CH_{Ar}), 128.5 (4CH_{Ar}), 128.6 (CH_{Ar}), 128.7 (CH_{Ar}), 128.7 (2CH_{Ar}), 130.6 (2CH_{Ar}), 130.7 (CH_{Ar}), 130.9 (CH_{Ar}), 131.4 (2C_{Ar}), 132.0 (C_{Ar}), 132.1 (C_{Ar}), 133.1 (d, C_{Ar}, $J_{C\text{-}P}$ = 0.9 Hz), 133.3 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.2 Hz), 133.3 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.7 Hz), 133.6 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.2 Hz), 138.4 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.3 Hz), 147.6 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 1.8 Hz), 148.6 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 5.5 Hz), 150.4 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 0.9 Hz), 150.7 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 4.9 Hz).

3,5-Bis-(*R*)-[(1,1'-binaphthyl-2,2'-diyl)phosphite]-5-deoxy-5-*N*-(*S*)-α-methylbenzylamino-1,2-*O*-isopropylidene-α-D-xylofuranose (**26g**)



Starting from (*R*)-BINOL (630 mg, 2.2 mmol), 5-deoxy-5-*N*-(*S*)-α-methylbenzylamino-1,2-*O*-isopropylidene-α-D-xylofuranose **24g** (294 mg, 1.0 mmol) and Et_3N (1.01 g, 10.0 mmol) in toluene (16 mL), the product **26g** was isolated as a white solid (570 mg, 62 %, R_f 0.15).

$[\alpha]_D^{24}$ = -386.4 (*c* 0.73, $CHCl_3$).

Anal. calcd for $C_{56}H_{45}NO_8P_2$: C, 72.96; H, 4.92; N, 1.52. Found: C, 73.07; H, 4.93; N, 1.44 %.

HRMS (ESI) calculated for $C_{56}H_{46}NO_8P_2$ 922.26932, found 922.26877.

HRMS (ESI) calculated for $C_{56}H_{45}NO_8P_2Na$ 944.25126, found 944.25027.

^{31}P{^{1}H} NMR (101 MHz, C_6D_6): δ (ppm) = 150.6 (d, $J_{P\text{-}P}$ = 17.1 Hz), 151.2 (d, $J_{P\text{-}P}$ = 17.1 Hz).

^{1}H NMR (250 MHz, C_6D_6): δ (ppm) = 1.04 (s, 3H, C(CH_3)$_2$), 1.36 (s, 3H, C(CH_3)$_2$), 1.53 (d, 3H, CHCH_3, $^{3}J_{H\text{-}H}$ = 7.2 Hz), 3.39-3.51 (m, 1H, H_A-5), 3.64-3.76 (ddd, 1H, H_B-5, $^{2}J_{5A\text{-}5B}$ = 15.1 Hz, J = 11.3 Hz, J = 3.4 Hz), 4.30-4.34 (m, 2H, H-3 and H-4), 4.55 (d, 1H, H-2, $^{3}J_{1\text{-}2}$ = 3.7 Hz), 4.90-5.02 (m, 1H, CHCH$_3$), 5.77 (d, 1H, H-1, $^{3}J_{1\text{-}2}$ = 3.7 Hz), 6.78-7.81 (m, 29H, CH-Ar).

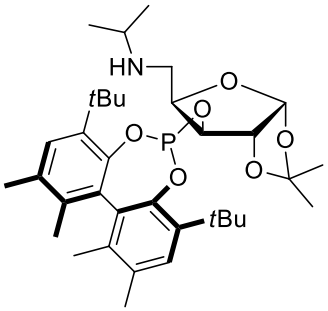
^{13}C NMR (63 MHz, C_6D_6): δ (ppm) = 20.7 (d, CHCH$_3$, $J_{C\text{-}P}$ = 12.1 Hz), 26.4 (C(CH$_3$)$_2$), 27.2 (C(CH$_3$)$_2$), 43.6 (d, C-5, $J_{5\text{-}P}$ = 18.9 Hz), 54.7 (d, CHCH$_3$, $J_{C\text{-}P}$ = 14.0 Hz), 78.6 (d, C-3, $J_{3\text{-}P}$ = 11.9 Hz), 80.7 (m, C-4), 85.0 (d, C-2, $J_{2\text{-}P}$ = 2.8 Hz), 105.2 (C-1), 111.8 (C(CH$_3$)$_2$), 121.7 (CH_{Ar}), 122.2 (CH_{Ar}), 122.8 (2CH_{Ar}), 123.3 (d, C_{Ar}, $J_{C\text{-}P}$ = 2.6 Hz), 123.3 (d, C_{Ar}, $J_{C\text{-}P}$ = 2.8 Hz), 124.5 (d, C_{Ar}, $J_{C\text{-}P}$ = 3.0 Hz), 124.6 (d, C_{Ar}, $J_{C\text{-}P}$ = 3.3 Hz), 125.0 (CH_{Ar}), 125.1 (CH_{Ar}), 125.2 (CH_{Ar}), 125.3 (CH_{Ar}), 126.5 (CH_{Ar}), 126.6 (CH_{Ar}), 126.6 (CH_{Ar}), 126.7 (CH_{Ar}), 127.2 (CH_{Ar}), 127.4 (2CH_{Ar}), 127.5 (CH_{Ar}), 127.6 (CH_{Ar}), 127.9 (2CH_{Ar}), 128.5 (CH_{Ar}), 128.6 (3CH_{Ar}), 128.7 (CH_{Ar}), 128.7 (CH_{Ar}), 130.2 (CH_{Ar}), 130.3 (CH_{Ar}), 130.7 (CH_{Ar}), 130.8 (CH_{Ar}), 131.2 (C_{Ar}), 131.5 (C_{Ar}), 132.0 (2C_{Ar}), 133.2 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.1 Hz), 133.3

(d, C_{Ar}, $J_{C\text{-}P}$ = 1.3 Hz), 133.5 (2C_{Ar}), 143.5 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.7 Hz), 147.6 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 1.8 Hz), 148.4 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 5.0 Hz), 150.2 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 6.2 Hz), 150.3 (C_{Ar}-O).

General procedure for the synthesis of amino xylose-based monophosphites **27a-c**

1.1 Eq of the corresponding chlorophosphite of the aromatic diol are dissolved in toluene (5 mL/1.1 mmol chlorophosphite) and pyridine (2.3 eq) is added. 1.0 Eq of azeotropically dried amino sugar **24b** is dissolved in toluene (5 mL/1.0 mmol substrate) and pyridine (2.3 eq) is added. The chlorophosphite solution is added slowly to the sugar solution at 0 °C over 5 min and the mixture is kept at this temperature for 5 min. The reaction solution is warmed to 80 °C and stirred for 16 h. After this time, the mixture is cooled to room temperature and concentrated *in vacuo*. The residue is purified by column chromatography (alumina, toluene/Et_3N = 97:3) to give **27a-c**.

3-(*S*)-[(3,3'-Di-*tert*-butyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diyl)phosphite]-5-deoxy-5-*N*-isopropylamino-1,2-*O*-isopropylidene-α-D-xylofuranose (**27a**)



Starting from (*S*)-(–)-5,5',6,6'-tetramethyl-3,3'-di-*tert*-butyl-1,1'-biphenyl-2,2'-diol (390 mg, 1.1 mmol), 5-Deoxy-5-*N*-isopropylamino-1,2-*O*-isopropylidene-α-D-xylofuranose **24b** (231 mg, 1.0 mmol) and pyridine (364 mg, 4.6 mmol) in toluene (10 mL), the product **27a** was isolated as a white solid (360 mg, 59 %, R_f 0.55).

$[\alpha]_D^{26}$ = -329.0 (*c* 1.00, $CHCl_3$).

Anal. calcd for $C_{35}H_{52}NO_6P$: C, 68.49; H, 8.54; N, 2.28. Found: C, 68.33; H, 8.87; N, 2.25 %.

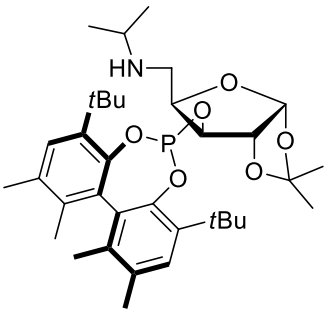
HRMS (EI) calculated for $C_{35}H_{52}NO_6P$ 613.35268, found 613.35339.

$^{31}P\{^1H\}$ NMR (121 MHz, C_6D_6): δ (ppm) = 140.9 (s).

^1H NMR (300 MHz, C_6D_6): δ (ppm) = 0.92 (d, 3H, $CH(CH_3)_2$, $^3J_{H\text{-}H}$ = 6.2 Hz), 0.97 (s, 3H, $C(CH_3)_2$), 0.98 (d, 3H, $CH(CH_3)_2$, $^3J_{H\text{-}H}$ = 6.2 Hz), 1.36 (s, 3H, $C(CH_3)_2$), 1.57 (br, 18H, $2C(CH_3)_3$), 1.70 (s, 3H, CH_3), 1.80 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.70 (m, 1H, $CH(CH_3)_2$), 3.05 (dd, 1H, H_A-5, $^2J_{5A\text{-}5B}$ = 11.8 Hz, $^3J_{4\text{-}5A}$ = 6.3 Hz), 3.11 (dd, 1H, H_B-5, $^2J_{5A\text{-}5B}$ = 11.8 Hz, $^3J_{4\text{-}5B}$ = 6.8 Hz), 4.08 (d, 1H, H-2, $^3J_{1\text{-}2}$ = 3.7 Hz), 4.42 (ddd, 1H, H-4, $^3J_{3\text{-}4}$ = 2.7 Hz), 4.91 (dd, 1H, H-3, $^3J_{3\text{-}P}$ = 8.1 Hz, J = 2.7 Hz), 5.78 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.8 Hz), 7.21 (s, 1H, CH-Ar), 7.23 (s, 1H, CH-Ar).

^{13}C NMR (75 MHz, C_6D_6): δ (ppm) = 16.6 (CH_3), 16.8 (CH_3), 20.4 (CH_3), 20.4 (CH_3), 23.1 ($CH(CH_3)_2$), 23.4 ($CH(CH_3)_2$), 26.0 ($C(CH_3)_2$), 26.8 ($C(CH_3)_2$), 31.7 (d, $C(CH_3)_3$, $J_{C\text{-}P}$ = 5.1 Hz), 31.9 ($C(CH_3)_3$), 35.0 ($C(CH_3)_3$), 35.2 ($C(CH_3)_3$), 46.1 (C-5), 49.3 ($CH(CH_3)_2$), 77.9 (C-3), 80.5 (d, C-4, $J_{4\text{-}P}$ = 5.6 Hz), 84.7 (C-2), 105.3 (C-1), 111.2 ($C(CH_3)_2$), 128.3 (CH_{Ar}), 128.5 (CH_{Ar}), 131.7 (d, C_{Ar}, $J_{C\text{-}P}$ = 3.2 Hz), 132.3 (d, C_{Ar}, $J_{C\text{-}P}$ = 0.8 Hz), 132.5 (d, C_{Ar}, $J_{C\text{-}P}$ = 5.2 Hz), 133.0 (C_{Ar}), 135.0 (d, C_{Ar}, $J_{C\text{-}P}$ = 0.9 Hz), 135.6 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.0 Hz), 138.2 (C_{Ar}), 138.6 (d, C_{Ar}, $J_{C\text{-}P}$ = 2.6 Hz), 145.5 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 5.5 Hz), 145.7 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 2.6 Hz).

3-(*R*)-[(3,3'-Di-*tert*-butyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diyl)phosphite]-5-deoxy-5-*N*-isopropylamino-1,2-*O*-isopropylidene-α-D-xylofuranose (**27b**)



Starting from (*R*)-(+)-5,5',6,6'-tetramethyl-3,3'-di-*tert*-butyl-1,1'-biphenyl-2,2'-diol (390 mg, 1.1 mmol), 5-Deoxy-5-*N*-isopropylamino-1,2-*O*-isopropylidene-α-D-xylofuranose **24b** (231 mg, 1.0 mmol) and pyridine (364 mg, 4.6 mmol) in toluene (10 mL), the product **27b** was isolated as a white solid (383 mg, 62 %, R_f 0.58).

$[\alpha]_D^{25}$ = +334.2 (*c* 1.00, $CHCl_3$).

Anal. calcd for $C_{35}H_{52}NO_6P$: C, 68.49; H, 8.54; N, 2.28. Found: C, 68.42; H, 8.36; N, 2.11 %.

HRMS (ESI) calculated for $C_{35}H_{53}NO_6P$ 614.3605, found 614.36048.

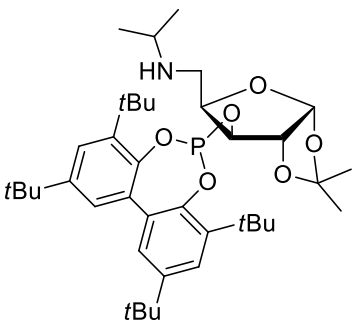
HRMS (ESI) calculated for $C_{35}H_{52}NO_6PNa$ 636.34245, found 636.34294.

$^{31}P\{^1H\}$ NMR (121 MHz, C_6D_6): δ (ppm) = 144.7 (s).

^1H NMR (300 MHz, C_6D_6): δ (ppm) = 0.77 (d, 3H, $CH(CH_3)_2$, $^3J_{H-H}$ = 6.2 Hz), 0.83 (d, 3H, $CH(CH_3)_2$, $^3J_{H-H}$ = 6.2 Hz), 1.09 (s, 3H, $C(CH_3)_2$), 1.37 (s, 3H, $C(CH_3)_2$), 1.50 (s, 9H, $C(CH_3)_3$), 1.56 (s, 9H, $C(CH_3)_3$), 1.71 (s, 3H, CH_3), 1.78 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.13 (s, 3H, CH_3), 2.34 (m, 1H, $CH(CH_3)_2$), 2.64 (dd, 1H, H_A-5, $^2J_{5A-5B}$ = 11.6 Hz, $^3J_{4-5A}$ = 7.3 Hz), 2.71 (dd, 1H, H_B-5, $^2J_{5A-5B}$ = 11.6 Hz, $^3J_{4-5A}$ = 6.5 Hz), 4.57 (ddd, 1H, H-4, $^3J_{3-4}$ = 2.8 Hz), 4.69 (d, 1H, H-2, $^3J_{1-2}$ = 3.0 Hz), 4.79 (dd, 1H, H-3, $^3J_{3-P}$ = 11.4 Hz, *J* = 2.8 Hz), 5.96 (d, 1H, H-1, $^3J_{1-2}$ = 3.7 Hz), 7.17 (s, 1H, CH-Ar), 7.26 (s, 1H, CH-Ar).

^{13}C NMR (63 MHz, C_6D_6): δ (ppm) = 16.3 (CH_3), 16.8 (CH_3), 20.4 (CH_3), 20.5 (CH_3), 23.2 ($CH(CH_3)_2$), 23.3 ($CH(CH_3)_2$), 26.5 ($C(CH_3)_2$), 27.0 ($C(CH_3)_2$), 31.6 (d, $C(CH_3)_3$, J_{C-P} = 5.1 Hz), 31.9 ($C(CH_3)_3$), 34.9 ($C(CH_3)_3$), 35.2 ($C(CH_3)_3$), 45.4 (C-5), 49.0 ($CH(CH_3)_2$), 76.9 (d, C-3, J_{3-P} = 7.8 Hz), 80.8 (d, C-4, J_{4-P} = 2.3 Hz), 85.0 (d, C-2, J_{2-P} = 2.8 Hz), 105.5 (C-1), 112.0 ($C(CH_3)_2$), 128.2 (CH_{Ar}), 128.6 (d, CH_{Ar}, J_{C-P} = 1.2 Hz), 131.3 (d, C_{Ar}, J_{C-P} = 3.3 Hz), 132.2 (d, C_{Ar}, J_{C-P} = 1.1 Hz), 132.6 (d, C_{Ar}, J_{C-P} = 5.2 Hz), 133.0 (d, C_{Ar}, J_{C-P} = 0.8 Hz), 134.4 (d, C_{Ar}, J_{C-P} = 1.3 Hz), 135.5 (d, C_{Ar}, J_{C-P} = 1.2 Hz), 138.1 (C_{Ar}), 138.4 (d, C_{Ar}, J_{C-P} = 2.7 Hz), 145.1 (d, C_{Ar}-O, J_{C-P} = 2.7 Hz), 145.2 (d, C_{Ar}-O, J_{C-P} = 6.6 Hz).

3-[(3,3',5,5'-Tetra-*tert*-butyl-1,1'-biphenyl-2,2'-diyl)phosphite]-5-deoxy-5-*N*-isopropylamino-1,2-*O*-isopropylidene-α-D-xylofuranose (**27c**)



Starting from 3,3',5,5'-tetra-*tert*-butyl-1,1'-biphenyl-2,2'-diol (904 mg, 2.2 mmol), 5-Deoxy-5-*N*-isopropylamino-1,2-*O*-isopropylidene-α-D-xylofuranose **24b** (462 mg, 2.0 mmol) and pyridine (728 mg, 9.2 mmol) in toluene (20 mL), the product **27c** was isolated as a white solid (950 mg, 71 %, R_f 0.50).

$[\alpha]_D^{25}$ = +15.5 (*c* 0.45, $CHCl_3$).

Anal. calcd for $C_{39}H_{60}NO_6P$: C, 69.93; H, 9.03; N, 2.09. Found: C, 68.89; H, 8.65; N, 2.23 %.

HRMS (ESI) calculated for $C_{39}H_{61}NO_6P$ 670.4231, found 670.42314.

HRMS (ESI) calculated for $C_{39}H_{60}NO_6PNa$ 692.40505, found 692.40366.

$^{31}P\{^{1}H\}$ NMR (121 MHz, C_6D_6): δ (ppm) = 149.0 (s).

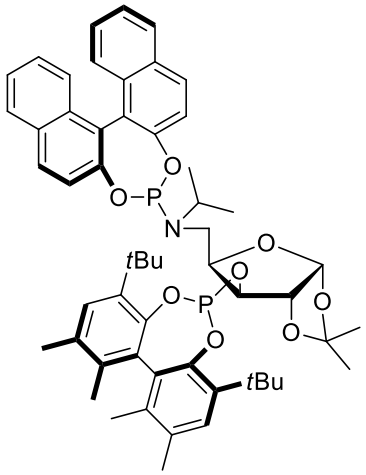
^{1}H NMR (300 MHz, C_6D_6): δ (ppm) = 0.89 (d, 3H, CH(CH_3)$_2$, $^{3}J_{H\text{-}H}$ = 6.2 Hz), 0.91 (d, 3H, CH(CH_3)$_2$, $^{3}J_{H\text{-}H}$ = 6.2 Hz), 1.05 (s, 3H, C(CH_3)$_2$), 1.25 (s, 9H, C(CH_3)$_3$), 1.29 (s, 9H, C(CH_3)$_3$), 1.38 (s, 3H, C(CH_3)$_2$), 1.57 (br, 18H, 2C(CH_3)$_3$), 2.62 (m, 1H, CH(CH_3)$_2$), 2.96 (dd, 1H, H_A-5, $^{2}J_{5A\text{-}5B}$ = 11.7 Hz, $^{3}J_{4\text{-}5A}$ = 6.4 Hz), 3.04 (dd, 1H, H_B-5, $^{2}J_{5A\text{-}5B}$ = 11.7 Hz, $^{3}J_{4\text{-}5B}$ = 6.9 Hz), 4.48-4.53 (m, 2H, H-2 and H-4), 4.92 (dd, 1H, H-3, $^{3}J_{3\text{-}P}$ = 9.8 Hz, J = 2.7 Hz), 5.85 (d, 1H, H-1, $^{3}J_{1\text{-}2}$ = 3.7 Hz), 7.37 (d, 1H, CH-Ar, $J_{H\text{-}P}$ = 2.5 Hz), 7.38 (d, 1H, CH-Ar, $J_{H\text{-}P}$ = 2.5 Hz), 7.59 (d, 1H, CH-Ar, $^{5}J_{H\text{-}P}$ = 2.5 Hz), 7.61 (d, 1H, CH-Ar, $^{5}J_{H\text{-}P}$ = 2.5 Hz).

^{13}C NMR (75 MHz, C_6D_6): δ (ppm) = 23.2 (CH(CH_3)$_2$), 23.4 (CH(CH_3)$_2$), 26.1 (C(CH_3)$_2$), 26.7 (C(CH_3)$_2$), 31.5 (d, C(CH_3)$_3$, $J_{C\text{-}P}$ = 3.1 Hz), 31.6 (C(CH_3)$_3$), 31.6 (2C(CH_3)$_3$), 34.7 (C(CH$_3$)$_3$), 34.7 (C(CH$_3$)$_3$), 35.7 (C(CH$_3$)$_3$), 35.8 (C(CH$_3$)$_3$), 46.1 (C-5), 49.2 (CH(CH$_3$)$_2$), 77.8 (d, C-3, $J_{3\text{-}P}$ = 4.4 Hz), 80.7 (d, C-4, $J_{4\text{-}P}$ = 4.4 Hz), 84.9 (d, C-2, $J_{2\text{-}P}$ = 2.0 Hz), 105.3 (C-1), 111.6 (C(CH$_3$)$_2$), 124.6 (2CH_{Ar}), 127.2 (2CH_{Ar}), 133.8 (d, C_{Ar}), 133.9 (d, C_{Ar}), 140.7 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.2 Hz), 140.9 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.7 Hz), 146.3 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 6.4 Hz), 146.3 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 6.0 Hz), 147.2 (d, 2C_{Ar}, $J_{C\text{-}P}$ = 5.7 Hz).

General procedure for the synthesis of amino xylose-based diphosphites **28a-f**

1.1 Eq of enantiopure BINOL are suspended in phosphorus trichloride (1.5 mL/1.0 mmol BINOL), 2-3 drops of *N*-methyl-2-pyrrolidone are added and the solution is heated to 75 °C for 5 min. The resulting HCl gas is derived from the reaction vessel by using a bubble counter (slight argon stream!). The now clear solution is cooled to room temperature, concentrated and dried azeotropically with toluene (three times). Thus, the *in situ* prepared chlorophosphite is dissolved in toluene (15 mL/1.1 mmol BINOL) and triethylamine is added (2.5 mmol/1.1 mmol BINOL). 1.0 Eq of azeotropically dried amino monophosphite **27a-c** is dissolved in toluene (15 mL/1.0 mmol substrate) and triethylamine (2.5 eq) is added. This solution is added slowly to the chlorophosphite solution at 0 °C over 5 min and the mixture is kept at this temperature for 5 min. The reaction solution is stirred at 50 °C for 16 h. After this time, the mixture is cooled to room temperature and concentrated *in vacuo*. The residue is purified by column chromatography (basic silica, toluene) to give **28a-f**.

3-(*S*)-[(3,3'-Di-*tert*-butyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diyl)phosphite]-5-(*S*)-[(1,1'-binaphthyl-2,2'-diyl)phosphite]-5-deoxy-5-*N*-isopropylamino-1,2-*O*-isopropylidene-α-D-xylofuranose (**28a**)



Starting from (*S*)-BINOL (128 mg, 0.45 mmol), 3-(*S*)-[(3,3'-di-*tert*-butyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diyl)phosphite]-5-deoxy-5-*N*-isopropylamino-1,2-*O*-isopropylidene-α-D-xylofuranose **27a** (250 mg, 0.41 mmol) and Et_3N (206 mg, 2.0 mmol) in toluene (12 mL), the product **28a** was isolated as a white solid (162 mg, 43 %, R_f 0.64).

$[\alpha]_D^{26}$ = -12.3 (*c* 0.35, $CHCl_3$).

Anal. calcd for $C_{55}H_{63}NO_8P_2$: C, 71.18; H, 6.84; N, 1.51. Found: C, 71.15; H, 6.87; N, 1.38 %.

HRMS (ESI) calculated for $C_{55}H_{64}NO_8P_2$ 928.41017, found 928.41011.

HRMS (ESI) calculated for $C_{55}H_{63}NO_8P_2Na$ 950.39211, found

950.39249.

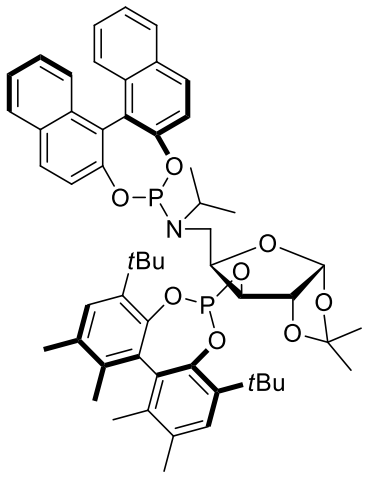
HRMS (ESI) calculated for $C_{55}H_{63}NO_8P_2K$ 966.36605, found 966.36708.

$^{31}P\{^1H\}$ NMR (121 MHz, C_6D_6): δ (ppm) = 138.3 (s), 153.1 (s).

^1H NMR (300 MHz, C_6D_6): δ (ppm) = 0.93 (d, 3H, CH(CH_3)$_2$, $^3J_{H\text{-}H}$ = 6.7 Hz), 1.04 (d, 3H, CH(CH_3)$_2$, $^3J_{H\text{-}H}$ = 6.8 Hz), 1.06 (s, 3H, C(CH_3)$_2$), 1.42 (s, 3H, C(CH_3)$_2$), 1.50 (s, 9H, C(CH_3)$_3$), 1.51 (s, 9H, C(CH_3)$_3$), 1.70 (s, 3H, CH_3), 1.83 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.14 (s, 3H, CH_3), 3.14 (ddd, 1H, H_A-5, J = 19.4 Hz, $^2J_{5A\text{-}5B}$ = 15.8 Hz, J = 8.3 Hz), 3.44 (ddd, 1H, H_B-5, $^2J_{5A\text{-}5B}$ = 15.7 Hz, J = 10.6 Hz, J = 2.5 Hz), 3.59-3.70 (m, 1H, CH(CH$_3$)$_2$, $^3J_{H\text{-}H}$ = 6.7 Hz), 4.57 (d, 1H, H-2, $^3J_{1\text{-}2}$ = 3.0 Hz), 4.64 (dd, 1H, H-3, $^3J_{3\text{-}P}$ = 9.8 Hz, J = 2.6 Hz), 4.71-4.74 (m, 1H, H-4), 5.96 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.7 Hz), 6.87-7.14 (m, 4H, CH-Ar), 7.20 (s, 1H, CH-Ar), 7.25 (s, 1H, CH-Ar), 7.42-7.72 (m, 8H, CH-Ar).

^{13}C NMR (75 MHz, C_6D_6): δ (ppm) = 16.6 (CH$_3$), 16.8 (CH$_3$), 20.4 (CH$_3$), 20.5 (CH$_3$), 22.3 (d, CH(CH_3)$_2$, $J_{C\text{-}P}$ = 3.0 Hz), 23.1 (d, CH(CH_3)$_2$, $J_{C\text{-}P}$ = 4.1 Hz), 26.5 (C(CH_3)$_2$), 27.1 (C(CH_3)$_2$), 31.6 (d, C(CH_3)$_3$), $J_{C\text{-}P}$ = 5.2 Hz), 31.7 (C(CH_3)$_3$), 34.9 (C(CH$_3$)$_3$), 35.1 (C(CH$_3$)$_3$), 42.5 (d, C-5, $J_{5\text{-}P}$ = 30.2 Hz), 47.3 (d, CH(CH$_3$)$_2$, $J_{C\text{-}P}$ = 6.3 Hz), 78.2 (d, C-3, $J_{C\text{-}P}$ = 4.1 Hz), 82.2 (m, C-4), 84.6 (d, C-2, $J_{C\text{-}P}$ = 4.2 Hz), 105.3 (C-1), 112.0 (C(CH$_3$)$_2$), 122.6 (d, CH$_{Ar}$, $J_{C\text{-}P}$ = 1.3 Hz), 122.8 (d, C$_{Ar}$, $J_{C\text{-}P}$ = 2.2 Hz), 123.0 (CH$_{Ar}$), 124.8 (CH$_{Ar}$), 124.8 (d, C$_{Ar}$), 124.9 (CH$_{Ar}$), 126.4 (CH$_{Ar}$), 126.5 (CH$_{Ar}$), 127.5 (CH$_{Ar}$), 127.6 (CH$_{Ar}$), 128.2 (CH$_{Ar}$), 128.7 (3CH$_{Ar}$), 130.1 (CH$_{Ar}$), 130.6 (CH$_{Ar}$), 131.2 (C$_{Ar}$), 131.4 (d, C$_{Ar}$, $J_{C\text{-}P}$ = 3.3 Hz), 131.9 (C$_{Ar}$), 132.3 (C$_{Ar}$), 132.6 (d, C$_{Ar}$, $J_{C\text{-}P}$ = 5.3 Hz), 133.0 (C$_{Ar}$), 133.3 (d, C$_{Ar}$, $J_{C\text{-}P}$ = 0.8 Hz), 133.5 (d, C$_{Ar}$, $J_{C\text{-}P}$ = 1.5 Hz), 134.7 (d, C$_{Ar}$, $J_{C\text{-}P}$ = 0.9 Hz), 135.6 (d, C$_{Ar}$, $J_{C\text{-}P}$ = 0.9 Hz), 138.0 (C$_{Ar}$), 138.5 (d, C$_{Ar}$, $J_{C\text{-}P}$ = 2.7 Hz), 145.3 (d, C$_{Ar}$-O), 145.4 (d, C$_{Ar}$-O), 150.5 (C$_{Ar}$), 151.0 (d, C$_{Ar}$-O, $J_{C\text{-}P}$ = 5.7 Hz).

3-(*R*)-[(3,3'-Di-*tert*-butyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diyl)phosphite]-5-(*S*)-[(1,1'-binaphthyl-2,2'-diyl)phosphite]-5-deoxy-5-*N*-isopropylamino-1,2-*O*-isopropylidene-α-D-xylofuranose (**28b**)



Starting from (*S*)-BINOL (128 mg, 0.45 mmol), 3-(*R*)-[(3,3'-di-*tert*-butyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diyl)phosphite]-5-deoxy-5-*N*-isopropylamino-1,2-*O*-isopropylidene-α-D-xylofuranose **27a** (250 mg, 0.41 mmol) and Et_3N (206 mg, 2.0 mmol) in toluene (12 mL), the product **28b** was isolated as a white solid (233 mg, 62 %, R_f 0.52).

$[\alpha]_D^{26}$ = +456.4 (*c* 0.56, $CHCl_3$).

Anal. calcd for $C_{55}H_{63}NO_8P_2$: C, 71.18; H, 6.84; N, 1.51. Found: C, 71.06; H, 6.80; N, 1.50 %.

HRMS (ESI) calculated for $C_{55}H_{64}NO_8P_2$ 928.41017, found 928.40949.

HRMS (ESI) calculated for $C_{55}H_{63}NO_8P_2Na$ 950.39211, found 950.39192.

HRMS (ESI) calculated for $C_{55}H_{63}NO_8P_2K$ 966.36605, found 966.3667.

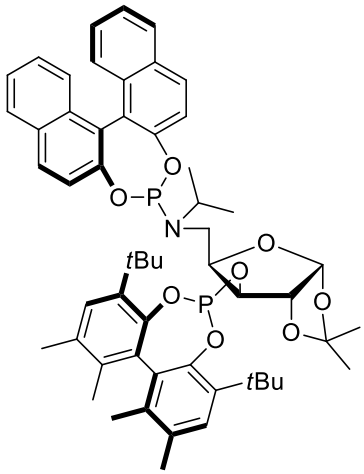
$^{31}P\{^1H\}$ NMR (121 MHz, C_6D_6): δ (ppm) = 140.1 (d, $J_{P\text{-}P}$ = 9.5 Hz), 149.8 (d, $J_{P\text{-}P}$ = 9.5 Hz).

^1H NMR (300 MHz, C_6D_6): δ (ppm) = 0.87 (s, 3H, C(CH_3)$_2$), 1.26 (d, 3H, CH(CH_3)$_2$, $^3J_{H\text{-}H}$ = 6.7 Hz), 1.30 (d, 3H, CH(CH_3)$_2$, $^3J_{H\text{-}H}$ = 6.8 Hz), 1.32 (s, 9H, C(CH_3)$_3$), 1.36 (s, 3H, C(CH_3)$_2$), 1.48 (s, 9H,

$C(CH_3)_3$), 1.65 (s, 3H, CH_3), 1.74 (s, 3H, CH_3), 2.00 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 3.14 (ddd, 1H, H_A-5, $^2J_{5A\text{-}5B}$ = 15.5 Hz, J = 9.9 Hz, J = 5.2 Hz), 3.65 (ddd, 1H, H_B-5, $^2J_{5A\text{-}5B}$ = 15.5 Hz, J = 5.9 Hz, J = 4.6 Hz), 3.81 (dq, 1H, C*H*$(CH_3)_2$, $^3J_{H\text{-}P}$ = 18.5 Hz, $^3J_{H\text{-}H}$ = 6.7 Hz), 3.95 (d, 1H, H-2, $^3J_{1\text{-}2}$ = 3.7 Hz), 4.48-4.52 (m, 1H, H-4), 4.69 (dd, 1H, H-3, $^3J_{3\text{-}P}$ = 6.3 Hz, J = 2.4 Hz), 5.49 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.7 Hz), 6.86-6.93 (m, 2H, CH-Ar), 7.00-7.19 (m, 4H, CH-Ar), 7.42-7.79 (m, 8H, CH-Ar).

^{13}C NMR (75 MHz, C_6D_6): δ (ppm) = 16.5 (CH_3), 16.7 (CH_3), 20.3 (CH_3), 20.3 (CH_3), 22.8 (d, CH(*C*H_3)$_2$, $J_{C\text{-}P}$ = 9.0 Hz), 23.5 (d, CH(*C*H_3)$_2$, $J_{C\text{-}P}$ = 6.7 Hz), 25.9 (C(*C*H_3)$_2$), 26.9 (C(*C*H_3)$_2$), 31.6 (d, C(*C*H_3)$_3$), $J_{C\text{-}P}$ = 5.1 Hz), 31.9 (C(*C*H_3)$_3$), 34.8 (*C*$(CH_3)_3$), 35.1 (*C*$(CH_3)_3$), 42.3 (d, C-5, $J_{5\text{-}P}$ = 8.1 Hz), 49.2 (d, *C*H$(CH_3)_2$, $J_{C\text{-}P}$ = 26.4 Hz), 77.3 (C-3), 82.7 (m, C-4), 84.7 (C-2), 105.2 (C-1), 111.2 (*C*$(CH_3)_2$), 122.3 (CH_{Ar}), 122.7 (d, CH_{Ar}, $J_{C\text{-}P}$ = 1.2 Hz), 123.1 (d, C_{Ar}, $J_{C\text{-}P}$ = 2.0 Hz), 125.0 (d, C_{Ar}), 124.9 (CH_{Ar}), 125.0 (CH_{Ar}), 126.4 (CH_{Ar}), 126.6 (CH_{Ar}), 127.5 (CH_{Ar}), 127.6 (CH_{Ar}), 128.2 (CH_{Ar}), 128.4 (CH_{Ar}), 128.6 (CH_{Ar}), 128.8 (CH_{Ar}), 130.5 (CH_{Ar}), 130.7 (CH_{Ar}), 131.3 (C_{Ar}), 131.9 (d, C_{Ar}, $J_{C\text{-}P}$ = 3.1 Hz), 132.0 (C_{Ar}), 132.1 (d, C_{Ar}, $J_{C\text{-}P}$ = 0.7 Hz), 132.4 (d, C_{Ar}, $J_{C\text{-}P}$ = 5.4 Hz), 132.8 (d, C_{Ar}, $J_{C\text{-}P}$ = 0.6 Hz), 133.4 (C_{Ar}), 133.5 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.4 Hz), 134.7 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.0 Hz), 135.4 (d, C_{Ar}, $J_{C\text{-}P}$ = 0.8 Hz), 138.5 (C_{Ar}), 138.6 (d, C_{Ar}, $J_{C\text{-}P}$ = 2.4 Hz), 145.4 (C_{Ar}-O), 145.4 (d, C_{Ar}-O), 150.4 (C_{Ar}-O), 150.8 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 4.7 Hz).

3-(*S*)-[(3,3'-Di-*tert*-butyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diyl)phosphite]-5-(*R*)-[(1,1'-binaphthyl-2,2'-diyl)phosphite]-5-deoxy-5-*N*-isopropylamino-1,2-*O*-isopropylidene-α-D-xylofuranose (**28c**)



Starting from (*R*)-BINOL (103 mg, 0.36 mmol), 3-(*S*)-[(3,3'-di-*tert*-butyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diyl)phosphite]-5-deoxy-5-*N*-isopropylamino-1,2-*O*-isopropylidene-α-D-xylofuranose **27b** (200 mg, 0.33 mmol) and Et_3N (165 mg, 1.6 mmol) in toluene (10 mL), the product **28c** was isolated as a white solid (230 mg, 76 %, R_f 0.52).

$[\alpha]_D^{27}$ = +23.5 (*c* 0.52, $CHCl_3$).

Anal. calcd for $C_{55}H_{63}NO_8P_2$: C, 71.18; H, 6.84; N, 1.51. Found: C, 71.01; H, 6.70; N, 1.59 %.

HRMS (ESI) calculated for $C_{55}H_{64}NO_8P_2$ 928.41017, found 928.40979.

HRMS (ESI) calculated for $C_{55}H_{63}NO_8P_2Na$ 950.39211, found 950.39186.

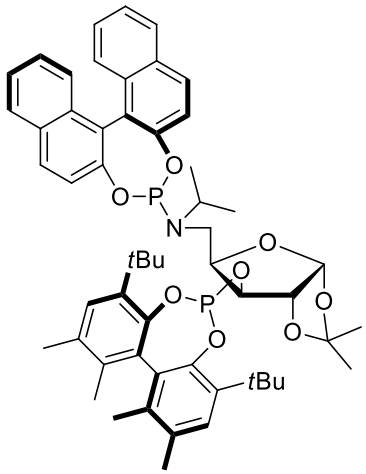
^{31}P{^{1}H} NMR (121 MHz, C_6D_6): δ (ppm) = 144.9 (s), 155.8 (s).

^{1}H NMR (300 MHz, C_6D_6): δ (ppm) = 0.95 (s, 3H, C$(CH_3)_2$), 1.07 (d, 3H, CH(C*H*$_3$)$_2$, $^3J_{H\text{-}H}$ = 6.8 Hz), 1.08 (d, 3H, CH(C*H*$_3$)$_2$, $^3J_{H\text{-}H}$ = 6.7 Hz), 1.41 (s, 3H, C$(CH_3)_2$), 1.51 (s, 9H, C$(CH_3)_3$), 1.58 (s, 9H, C$(CH_3)_3$), 1.68 (s, 3H, CH_3), 1.79 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 3.62-3.73 (m, 3H, C*H*$(CH_3)_2$ and 2H-5), 4.12 (d, 1H, H-2, $^3J_{1\text{-}2}$ = 3.7 Hz), 4.59-4.64 (m, 1H, H-4), 4.85 (dd, 1H, H-3, $^3J_{3\text{-}P}$ = 7.0 Hz, J = 2.5 Hz), 5.67 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.7 Hz), 6.87-7.14 (m, 4H, CH-Ar), 7.19 (s, 1H, CH-Ar), 7.22 (s, 1H, CH-Ar), 7.43-7.74 (m, 8H, CH-Ar).

^{13}C NMR (75 MHz, C_6D_6): δ (ppm) = 16.5 (CH_3), 16.8 (CH_3), 20.3 (CH_3), 20.4 (CH_3), 22.4 (d, CH(*C*H_3)$_2$, $J_{C\text{-}P}$ = 4.6 Hz), 23.3 (d, CH(*C*H_3)$_2$, $J_{C\text{-}P}$ = 5.0 Hz), 26.0 (C(*C*H_3)$_2$), 26.9 (C(*C*H_3)$_2$), 31.7 (d, C(*C*H_3)$_3$), $J_{C\text{-}P}$ = 5.1 Hz), 31.8 (C(*C*H_3)$_3$), 35.0 (*C*$(CH_3)_3$), 35.1 (*C*$(CH_3)_3$), 42.3 (d, C-5, $J_{5\text{-}P}$ = 29.4 Hz), 47.5 (d, *C*H$(CH_3)_2$, $J_{C\text{-}P}$ = 7.9 Hz), 77.9 (C-3), 80.7 (m, C-4), 84.8 (d, C-2,

$J_{C\text{-}P}$ = 2.0 Hz), 105.1 (C-1), 111.2 ($C(CH_3)_2$), 122.7 (CH_{Ar}), 122.8 (CH_{Ar}), 123.0 (d, C_{Ar}, $J_{C\text{-}P}$ = 2.1 Hz), 124.7 (d, C_{Ar}, $J_{C\text{-}P}$ = 5.4 Hz), 124.8 (CH_{Ar}), 124.9 (CH_{Ar}), 126.4 (CH_{Ar}), 126.5 (CH_{Ar}), 127.5 ($2CH_{Ar}$), 128.3 (CH_{Ar}), 128.5 ($2CH_{Ar}$), 128.7 (CH_{Ar}), 130.0 (CH_{Ar}), 130.7 (CH_{Ar}), 131.1 (C_{Ar}), 131.7 (d, C_{Ar}, $J_{C\text{-}P}$ = 3.1 Hz), 131.9 (C_{Ar}), 132.3 (d, C_{Ar}, $J_{C\text{-}P}$ = 0.7 Hz), 132.4 (d, C_{Ar}, $J_{C\text{-}P}$ = 5.2 Hz), 133.1 (C_{Ar}), 133.4 (d, C_{Ar}, $J_{C\text{-}P}$ = 0.9 Hz), 133.5 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.6 Hz), 134.9 (d, C_{Ar}, $J_{C\text{-}P}$ = 0.8 Hz), 135.7 (d, C_{Ar}, $J_{C\text{-}P}$ = 0.8 Hz), 138.5 (C_{Ar}), 138.6 (d, C_{Ar}, $J_{C\text{-}P}$ = 2.6 Hz), 145.4 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 5.6 Hz), 145.6 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 2.6 Hz), 150.6 (C_{Ar}-O), 150.8 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 5.8 Hz).

3-(*R*)-[(3,3'-Di-*tert*-butyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diyl)phosphite]-5-(*R*)-[(1,1'-binaphthyl-2,2'-diyl)phosphite]-5-deoxy-5-*N*-isopropylamino-1,2-*O*-isopropylidene-α-D-xylofuranose (**28d**)



Starting from (*R*)-BINOL (132 mg, 0.46 mmol), 3-(*R*)-[(3,3'-di-*tert*-butyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diyl)phosphite]-5-deoxy-5-*N*-isopropylamino-1,2-*O*-isopropylidene-α-D-xylofuranose **27b** (260 mg, 0.42 mmol) and Et_3N (214 mg, 2.2 mmol) in toluene (12 mL), the product **28d** was isolated as a white solid (285 mg, 73 %, R_f 0.58).

$[\alpha]_D^{26}$ = -356.0 (*c* 0.42, $CHCl_3$).

Anal. calcd for $C_{55}H_{63}NO_8P_2$: C, 71.18; H, 6.84; N, 1.51. Found: C, 70.78; H, 6.79; N, 1.51 %.

HRMS (ESI) calculated for $C_{55}H_{64}NO_8P_2$ 928.41017, found 928.41003.

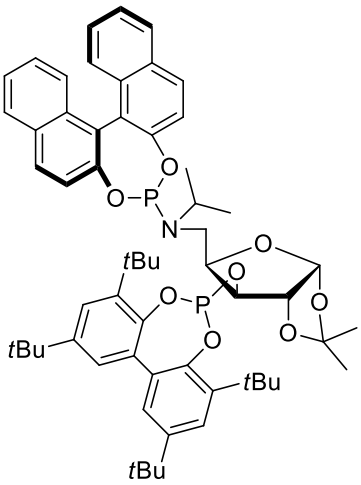
HRMS (ESI) calculated for $C_{55}H_{63}NO_8P_2Na$ 950.39211, found 950.39183.

$^{31}P\{^1H\}$ NMR (121 MHz, C_6D_6): δ (ppm) = 144.9 (s), 155.8 (s).

^1H NMR (300 MHz, C_6D_6): δ = 0.96 (d, 6H, $CH(CH_3)_2$, $^3J_{H\text{-}H}$ = 6.6 Hz), 1.07 (s, 3H, $C(CH_3)_2$), 1.46 (s, 3H, $C(CH_3)_2$), 1.50 (s, 9H, $C(CH_3)_3$), 1.57 (s, 9H, $C(CH_3)_3$), 1.69 (s, 3H, CH_3), 1.76 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 3.12 (ddd, 1H, H_A-5, $^2J_{5A\text{-}5B}$ = 15.8 Hz, *J* = 10.8 Hz, *J* = 7.5 Hz), 3.32-3.44 (ddd, 1H, H_B-5, *J* = 18.0 Hz, $^2J_{5A\text{-}5B}$ = 15.8 Hz, *J* = 2.7 Hz), 3.56 (m, 1H, $CH(CH_3)_2$), 4.54-4.58 (m, 1H, H-4), 4.64 (m, 1H, H-2), 4.65 (dd, 1H, H-3, $^3J_{3\text{-}P}$ = 10.0 Hz, *J* = 2.6 Hz), 5.85 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.7 Hz), 6.87-7.14 (m, 5H, CH-Ar) 7.35 (s, 1H, CH-Ar), 7.46-7.55 (m, 2H, CH-Ar), 7.52 (s, 1H, CH-Ar), 7.59 (s, 1H, CH-Ar), 7.62-7.67 (m, 2H, CH-Ar), 7.70-7.80 (m, 2H, CH-Ar).

^{13}C NMR (75 MHz, C_6D_6): δ (ppm) = 16.6 (CH_3), 16.8 (CH_3), 20.4 (CH_3), 20.6 (CH_3), 22.4 (d, $CH(CH_3)_2$, $J_{C\text{-}P}$ = 4.2 Hz), 22.8 (d, $CH(CH_3)_2$, $J_{C\text{-}P}$ = 4.8 Hz), 26.5 ($C(CH_3)_2$), 27.1 ($C(CH_3)_2$), 31.5 (d, $C(CH_3)_3$ $J_{C\text{-}P}$ = 4.9 Hz) 31.9 ($C(CH_3)_3$), 34.9 ($C(CH_3)_3$), 35.2 ($C(CH_3)_3$), 42.7 (d, C-5, $J_{5\text{-}P}$ = 31.6 Hz), 47.5 ($CH(CH_3)_2$), 77.7 (d, C-3, $J_{3\text{-}P}$ = 7.1 Hz), 82.1 (br, C-4), 84.9 (d, C-2, $J_{2\text{-}P}$ = 4.2 Hz), 105.2 (C-1), 111.8 ($C(CH_3)_2$), 122.6 (d, CH_{Ar}, $J_{C\text{-}P}$ = 1.2 Hz), 123.0 (CH_{Ar}), 123.2 (d, C_{Ar}, $J_{C\text{-}P}$ = 2.2 Hz), 124.7 (d, C_{Ar}, $J_{C\text{-}P}$ = 5.2 Hz), 124.4 (CH_{Ar}), 124.9 (CH_{Ar}), 126.4 (CH_{Ar}), 126.5 (CH_{Ar}), 127.5 (CH_{Ar}), 127.5 (CH_{Ar}), 128.2 (CH_{Ar}), 128.5 (CH_{Ar}), 128.7 (CH_{Ar}), 128.8 (CH_{Ar}), 129.9 (CH_{Ar}), 130.6 (CH_{Ar}), 131.1 (C_{Ar}), 131.4 (d, C_{Ar}, $J_{C\text{-}P}$ = 3.3 Hz), 131.9 (C_{Ar}), 132.3 (C_{Ar}), 132.6 (d, C_{Ar}, $J_{C\text{-}P}$ = 5.1 Hz), 133.0 (d, C_{Ar}, $J_{C\text{-}P}$ = 0.7 Hz), 133.4 (d, C_{Ar}, $J_{C\text{-}P}$ = 0.9 Hz), 133.5 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.4 Hz), 134.8 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.0 Hz), 135.6 (d, C_{Ar}, $J_{C\text{-}P}$ = 0.9 Hz), 138.0 (C_{Ar}), 138.4 (d, C_{Ar}, $J_{C\text{-}P}$ = 2.7 Hz), 145.1 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 6.5 Hz), 145.4 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 2.7 Hz), 150.6 (C_{Ar}-O), 150.8 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 6.0 Hz).

3-[(3,3',5,5'-Tetra-*tert*-butyl-1,1'-biphenyl-2,2'-diyl)phosphite]-5-(*S*)-[(1,1'-binaphthyl-2,2'-diyl)phosphite]-5-deoxy-5-*N*-isopropylamino-1,2-*O*-isopropylidene-α-D-xylofuranose (**28e**)



Starting from (*S*)-BINOL (158 mg, 0.55 mmol), 3-[(3,3',5,5'-tetra-*tert*-butyl-1,1'-biphenyl-2,2'-diyl)phosphite]-5-deoxy-5-*N*-isopropylamino-1,2-*O*-isopropylidene-α-D-xylofuranose **27c** (335 mg, 0.50 mmol) and Et_3N (253 mg, 2.6 mmol) in toluene (15 mL), the product **28e** was isolated as a white solid (350 mg, 71 %, R_f 0.67).

$[\alpha]_D^{25}$ = +353.8 (*c* 0.48, $CHCl_3$).

Anal. calcd for $C_{59}H_{71}NO_8P_2$: C, 72.00; H, 7.27; N, 1.42. Found: C, 71.96; H, 7.67; N, 1.41 %.

HRMS (ESI) calculated for $C_{59}H_{72}NO_8P_2$ 984.47277, found 984.47214.

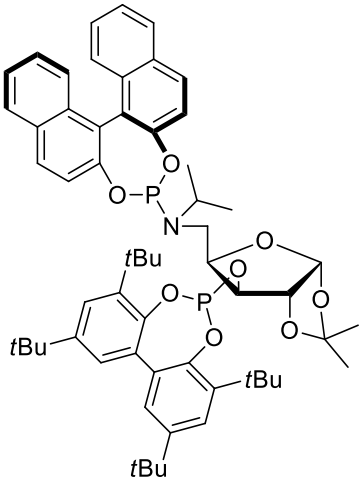
HRMS (ESI) calculated for $C_{59}H_{71}NO_8P_2Na$ 1006.45471, found 1006.45459.

$^{31}P\{^1H\}$ NMR (121 MHz, C_6D_6): δ (ppm) = 150.3 (d, J_{P-P} = 5.3 Hz), 153.9 (d, J_{P-P} = 5.3 Hz).

^1H NMR (300 MHz, C_6D_6): δ (ppm) = 0.92 (s, 3H, $C(CH_3)_2$), 1.24 (s, 9H, $C(CH_3)_3$), 1.26 (s, 9H, $C(CH_3)_3$), 1.28 (d, 3H, $CH(CH_3)_2$, $^3J_{H-H}$ = 6.7 Hz), 1.32 (d, 3H, $CH(CH_3)_2$, $^3J_{H-H}$ = 6.7 Hz), 1.36 (s, 9H, $C(CH_3)_3$), 1.37 (s, 3H, $C(CH_3)_2$), 1.53 (s, 9H, $C(CH_3)_3$), 3.17 (ddd, 1H, H_B-5, $^2J_{5A-5B}$ = 15.6 Hz, *J* = 9.7 Hz, *J* = 6.1 Hz), 3.58-3.66 (ddd, 1H, H_B-5, $^2J_{5A-5B}$ = 15.5 Hz, *J* = 6.1 Hz, *J* = 3.5 Hz), 3.84 (m, 1H, $CH(CH_3)_2$), 4.28 (d, 1H, H-2, $^3J_{1-2}$ = 3.6 Hz), 4.54-4.58 (m, 1H, H-4), 4.66 (dd, 1H, H-3, $^3J_{3-P}$ = 7.9 Hz, *J* = 2.4 Hz), 5.51 (d, 1H, H-1, $^3J_{3-P}$ = 3.6 Hz), 6.84-7.14 (m, 4H, CH-Ar), 7.34 (s, 1H, CH-Ar), 7.34 (s, 1H, CH-Ar), 7.43-7.65 (m, 9H, CH-Ar), 7.75-7.78 (m, 1H, CH-Ar).

^{13}C NMR (75 MHz, C_6D_6): δ (ppm) = 22.9 (d, $CH(CH_3)_2$, J_{C-P} = 9.2 Hz), 23.6 (d, $CH(CH_3)_2$, J_{C-P} = 6.9 Hz), 26.4 ($C(CH_3)_2$), 27.0 ($C(CH_3)_2$), 31.4 (d, $C(CH_3)_3$, J_{C-P} = 4.3 Hz), 31.6 ($2C(CH_3)_3$), 31.7 ($C(CH_3)_3$), 34.7 ($C(CH_3)_3$), 34.7 ($C(CH_3)_3$), 35.5 ($C(CH_3)_3$, 35.8 ($C(CH_3)_3$), 42.8 (d, C-5, J_{5-P} = 7.0 Hz), 49.3 (d, $CH(CH_3)_2$, J_{C-P} = 26.0 Hz), 77.3 (d, C-3, J_{3-P} = 4.3 Hz), 82.9 (m, C-4), 84.7 (C-2), 105.3 (C-1), 111.6 ($C(CH_3)_2$), 122.3 (CH_{Ar}), 122.6 (d, CH_{Ar}, J_{C-P} = 1.2 Hz), 123.0 (d, C_{Ar}, J_{C-P} = 2.1 Hz), 124.4 (CH_{Ar}), 124.6 (CH_{Ar}), 124.9 (CH_{Ar}), 125.0 (d, C_{Ar}, J_{C-P} = 5.3 Hz), 125.0 (CH_{Ar}), 126.4 (CH_{Ar}), 126.5 (CH_{Ar}), 126.9 (CH_{Ar}), 127.0 (CH_{Ar}), 127.4 (CH_{Ar}), 127.6 (CH_{Ar}), 128.6 (CH_{Ar}), 128.8 (CH_{Ar}), 130.6 (CH_{Ar}), 130.7 (CH_{Ar}), 131.3 (C_{Ar}), 132.0 (C_{Ar}), 133.4 (d, C_{Ar}), 133.4 (d, C_{Ar}), 133.5 (d, C_{Ar}, J_{C-P} = 1.7 Hz), 134.2 (d, C_{Ar}, J_{C-P} = 4.7 Hz), 140.9 (C_{Ar}), 141.0 (d, C_{Ar}, J_{C-P} = 2.1 Hz), 145.8 (d, C_{Ar}-O, J_{C-P} = 4.0 Hz), 146.7 (d, C_{Ar}-O, J_{C-P} = 8.7 Hz), 146.8 (C_{Ar}), 147.2 (C_{Ar}), 150.4 (C_{Ar}-O), 150.8 (d, C_{Ar}-O, J_{C-P} = 4.8 Hz).

3-[(3,3',5,5'-Tetra-*tert*-butyl-1,1'-biphenyl-2,2'-diyl)phosphite]-5-(*R*)-[(1,1'-binaphthyl-2,2'-diyl)phosphite]-5-deoxy-5-*N*-isopropylamino-1,2-*O*-isopropylidene-α-D-xylofuranose (**28f**)



Starting from (*R*)-BINOL (158 mg, 0.55 mmol), 3-[(3,3',5,5'-tetra-*tert*-butyl-1,1'-biphenyl-2,2'-diyl)phosphite]-5-deoxy-5-*N*-isopropylamino-1,2-*O*-isopropylidene-α-D-xylofuranose **27c** (335 mg, 0.50 mmol) and Et_3N (253 mg, 2.5 mmol) in toluene (15 mL), the product **28f** was isolated as a white solid (440 mg, 89 %, R_f 0.67).

$[\alpha]_D^{27}$ = -99.7 (*c* 0.68, $CHCl_3$).

Anal. calcd for $C_{59}H_{71}NO_8P_2$: C, 72.00; H, 7.27; N, 1.42. Found: C, 72.23; H, 7.98; N, 1.38 %.

HRMS (ESI) calculated for $C_{59}H_{72}NO_8P_2$ 984.47277, found 984.47261.

HRMS (ESI) calculated for $C_{59}H_{71}NO_8P_2Na$ 1006.45471, found 1006.45455.

$^{31}P\{^1H\}$ NMR (101 MHz, C_6D_6): δ (ppm) = 149.3 (d, J_{P-P} = 9.5 Hz), 154.6 (d, J_{P-P} = 9.6 Hz).

^1H NMR (250 MHz, C_6D_6): δ (ppm) = 1.03 (s, 3H, $C(CH_3)_2$), 1.06 (d, 3H, $CH(CH_3)_2$, $^3J_{H-H}$ = 7.0 Hz), 1.06 (d, 3H, $CH(CH_3)_2$, $^3J_{H-H}$ = 6.6 Hz), 1.26 (s, 18H, $2C(CH_3)_3$), 1.45 (s, 3H, $C(CH_3)_2$), 1.53 (s, 9H, $C(CH_3)_3$), 1.58 (s, 9H, $C(CH_3)_3$), 3.51-3.76 (m, 3H, $CH(CH_3)_2$ and 2H-5), 4.53 (d, 1H, H-2, $^3J_{1-2}$ = 3.6 Hz), 4.58-4.63 (m, 1H, H-4), 4.78 (dd, 1H, H-3, $^3J_{3\,P}$ = 8.6 Hz, *J* = 2.4 Hz), 5.72 (d, 1H, H-1, $^3J_{1-2}$ = 3.7 Hz), 6.84-7.14 (m, 4H, CH-Ar), 7.31-7.32 (m, 1H, CH-Ar), 7.37-7.38 (m, 1H, CH-Ar), 7.43-7.63 (m, 8H, CH-Ar), 7.69-7.76 (m, 2H, CH-Ar).

^{13}C NMR (63 MHz, C_6D_6): δ (ppm) = 22.5 (d, $CH(CH_3)_2$, J_{C-P} = 4.9 Hz), 23.3 (d, $CH(CH_3)_2$, J_{C-P} = 5.1 Hz), 26.5 ($C(CH_3)_2$), 27.1 ($C(CH_3)_2$), 31.6 (4 $C(CH_3)_3$), 34.7 ($2C(CH_3)_3$), 35.7 ($C(CH_3)_3$), 35.8 ($C(CH_3)_3$), 42.6 (d, C-5, J_{5-P} = 28.9 Hz), 47.6 (d, $CH(CH_3)_2$, J_{C-P} = 8.2 Hz), 77.9 (d, C-3, J_{3-P} = 3.9 Hz), 81.2 (m, C-4), 84.8 (d, C-2, J_{2-P} = 3.2 Hz), 105.1 (C-1), 111.6 ($C(CH_3)_2$), 122.7 (d, CH_{Ar}, J_{C-P} = 1.4 Hz), 122.9 (CH_{Ar}), 123.1 (d, C_{Ar}, J_{C-P} = 2.2 Hz), 124.5 (CH_{Ar}), 124.6 (CH_{Ar}), 124.6 (d, C_{Ar}), 124.8 (CH_{Ar}), 124.9 (CH_{Ar}), 126.3 (CH_{Ar}), 126.4 (CH_{Ar}), 127.1 (CH_{Ar}), 127.3 (CH_{Ar}), 127.5 ($2CH_{Ar}$), 128.5 (CH_{Ar}), 128.7 (CH_{Ar}), 130.0 (CH_{Ar}), 130.7 (CH_{Ar}), 131.1 (C_{Ar}), 131.9 (C_{Ar}), 133.4 (d, C_{Ar}, J_{C-P} = 1.1 Hz), 133.5 (d, C_{Ar}, J_{C-P} = 1.5 Hz), 133.7 (d, C_{Ar}, J_{C-P} = 3.7 Hz), 133.8 (d, C_{Ar}, J_{C-P} = 4.0 Hz), 140.8 (C_{Ar}), 140.8 (d, C_{Ar}), 146.3 (d, C_{Ar}-O, J_{C-P} = 4.3 Hz), 146.3 (d, C_{Ar}-O, J_{C-P} = 5.0 Hz), 147.2 ($2C_{Ar}$), 150.6 (C_{Ar}-O), 150.7 (d, C_{Ar}-O, J_{C-P} = 6.0 Hz).

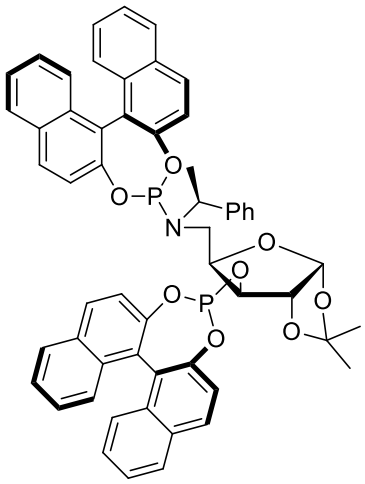
General procedure for the synthesis of amino xylose-based mixed diphosphites **28g-i**

1.1 Eq of enantiopure BINOL are suspended in phosphorus trichloride (1.5 mL/1.0 mmol BINOL), 2-3 drops of *N*-methyl-2-pyrrolidone are added and the solution is heated to 75 °C for 5 min. The resulting HCl gas is derived from the reaction vessel by using a bubble counter (slight argon stream!). The now clear solution is cooled to room temperature, concentrated and dried azeotropically with toluene (three times). Thus, the *in situ* prepared chlorophosphite is dissolved in toluene (5 mL/1.1 mmol BINOL) and pyridine (2.3 eq) is added. 1.0 Eq of azeotropically dried amino sugar **24g** is dissolved in toluene (5 mL/1.0 mmol substrate) and pyridine (2.3 eq) is added. The chlorophosphite solution is added slowly to the sugar solution at 0 °C over 5 min and the mixture is kept at this temperature for 5 min. The reaction solution is warmed to 80 °C and stirred for 16 h. After this time, the mixture is cooled to room temperature and concentrated *in vacuo*. Because the residue can not be purified by column

chromatography or recrystallization, crude products **27d,e** are used in the next step without further purification.

1.1 Eq of the corresponding chlorophosphite of the aromatic diol are dissolved in toluene (10 mL/1.1 mmol chlorophosphite) and triethylamine (2.0 eq) is added. 1.0 Eq of the crude **27d,e** is dissolved in toluene (10 mL/1.0 mmol substrate) and triethylamine (2.0 eq) is added. The chlorophosphite solution is added slowly to the sugar solution at 0 °C over 5 min and the mixture is kept at this temperature for 5 min. The reaction solution is warmed to 50 °C and stirred for 16 h. After this time, the mixture is cooled to room temperature and concentrated *in vacuo*. The residue is purified by column chromatography (basic silica, toluene) to give **28g-i**.

3-(*S*)-[(1,1'-binaphthyl-2,2'-diyl)phosphite]-5-(*R*)-[(1,1'-binaphthyl-2,2'-diyl)phosphite]-5-deoxy-5-*N*-α-methyl-benzylamino-1,2-*O*-isopropylidene-α-D-xylofuranose (**28g**)



Starting from (*S*)-BINOL (158 mg, 0.55 mmol), (*R*)-BINOL (158 mg, 0.55 mmol), 5-Deoxy-5-*N*-(*S*)-α-methylbenzylamino-1,2-*O*-isopropylidene-α-D-xylofuranose **27d** (147 mg, 0.5 mmol), pyridine (182 mg, 2.3 mmol) and Et_3N (202 mg, 2.0 mmol) in toluene, the product **28g** was isolated as a white solid (161 mg, 35 %, R_f 0.28).

$[\alpha]_D^{26}$ = +12.1 (*c* 0.37, $CHCl_3$).

Anal. calcd for $C_{56}H_{45}NO_8P_2$: C, 72.96; H, 4.92; N, 1.52. Found: C, 73.09; H, 4.82; N, 1.30 %.

HRMS (ESI) calculated for $C_{56}H_{46}NO_8P_2$ 922.26932, found 922.26902.

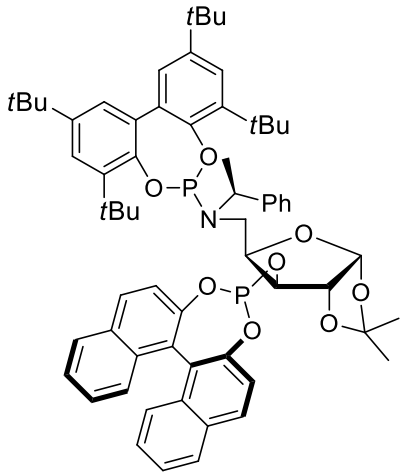
HRMS (ESI) calculated for $C_{56}H_{45}NO_8P_2Na$ 944.25126, found 944.2511.

$^{31}P\{^1H\}$ NMR (121 MHz, C_6D_6): δ (ppm) = 147.4 (d, $J_{P\text{-}P}$ = 4.8 Hz), 148.7 (brs).

^1H NMR (300 MHz, C_6D_6): δ (ppm) = 0.96 (s, 3H, $C(CH_3)_2$), 1.40 (s, 3H, $C(CH_3)_2$), 1.62 (d, 3H, $CHCH_3$, $^3J_{H\text{-}H}$ = 6.7 Hz), 3.32-3.42 (m, 1H, H_A-5), 3.75 (ddd, 1H, H_B-5, $^2J_{5A\text{-}5B}$ = 15.5 Hz, *J* = 9.1 Hz, *J* = 2.8 Hz), 4.22-4.26 (m, 2H, H-2 and H-3), 4.36-4.40 (m, 1H, H-4), 4.98 (m, 1H, $CHCH_3$), 5.60 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.7 Hz), 6.81-6.91 (m, 4H, CH-Ar), 7.00-7.16 (m, 5H, CH-Ar), 7.19-7.80 (m, 20H, CH-Ar).

^{13}C NMR (63 MHz, C_6D_6): δ (ppm) = 21.5 (d, $CHCH_3$, $J_{C\text{-}P}$ = 15.7 Hz), 26.5 ($C(CH_3)_2$), 27.1 ($C(CH_3)_2$), 42.6 (d, C-5, $J_{5\text{-}P}$ = 10.9 Hz), 55.6 ($CHCH_3$), 78.8 (d, C-3, $J_{3\text{-}P}$ = 13.2 Hz), 81.0 (m, C-4), 84.7 (d, C-2, $J_{2\text{-}P}$ = 2.2 Hz), 105.4 (C-1), 111.5 ($C(CH_3)_2$), 121.9 (CH_{Ar}), 122.3 (CH_{Ar}), 122.6 (CH_{Ar}), 122.7 (CH_{Ar}), 123.0 (d, C_{Ar}, $J_{C\text{-}P}$ = 2.6 Hz), 123.4 (d, C_{Ar}, $J_{C\text{-}P}$ = 2.2 Hz), 124.5 (d, C_{Ar}, $J_{C\text{-}P}$ = 5.1 Hz), 124.7 (d, C_{Ar}, $J_{C\text{-}P}$ = 5.1 Hz), 125.0 (CH_{Ar}), 125.1 (CH_{Ar}), 125.1 (CH_{Ar}), 125.3 (CH_{Ar}), 126.5 ($2CH_{Ar}$), 126.7 (CH_{Ar}), 126.8 (CH_{Ar}), 127.2 ($2CH_{Ar}$), 127.5 ($2CH_{Ar}$), 127.6 (CH_{Ar}), 127.8 (CH_{Ar}), 127.8 (CH_{Ar}), 128.4 (CH_{Ar}), 128.6 ($4CH_{Ar}$), 128.7 (CH_{Ar}), 130.3 (CH_{Ar}), 130.4 (CH_{Ar}), 130.7 (CH_{Ar}), 131.0 (CH_{Ar}), 131.1 (C_{Ar}), 131.6 (C_{Ar}), 132.0 ($2C_{Ar}$), 133.0 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.4 Hz), 133.4 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.3 Hz), 133.5 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.6 Hz), 133.6 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.2 Hz), 143.8 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.7 Hz), 147.7 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 2.5 Hz), 148.4 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 5.3 Hz), 150.1 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 6.4 Hz), 150.3 (C_{Ar}-O).

3-(*S*)-[(1,1'-binaphthyl-2,2'-diyl)phosphite]-5-[(3,3',5,5'-tetra-*tert*-butyl-1,1'-biphenyl-2,2'-diyl)phosphite]-5-deoxy-5-*N*-α-methyl-benzylamino-1,2-*O*-isopropylidene-α-D-xylofuranose (**28h**)



Starting from (*S*)-BINOL (158 mg, 0.55 mmol), 3,3',5,5'-tetra-*tert*-butyl-(1,1'-biphenyl)-2,2'-diol (226 mg, 0.55 mmol), 5-deoxy-5-*N*-(*S*)-α-methylbenzylamino-1,2-*O*-isopropylidene-α-D-xylofuranose **27d** (147 mg, 0.5 mmol), pyridine (182 mg, 2.3 mmol) and Et_3N (202 mg, 2.0 mmol) in toluene, the product **28h** was isolated as a white solid (125 mg, 24 %, R_f 0.58).

$[\alpha]_D^{24}$ = +85.7 (*c* 0.47, $CHCl_3$).

Anal. calcd for $C_{64}H_{73}NO_8P_2$: C, 73.47; H, 7.03; N, 1.34.Found: C, 73.77; H, 7.06; N, 1.10 %.

HRMS (ESI) calculated for $C_{64}H_{74}NO_8P_2$ 1046.48842, found 1046.48817.

HRMS (ESI) calculated for $C_{64}H_{73}NO_8P_2Na$ 1068.47036, found 1068.47042.

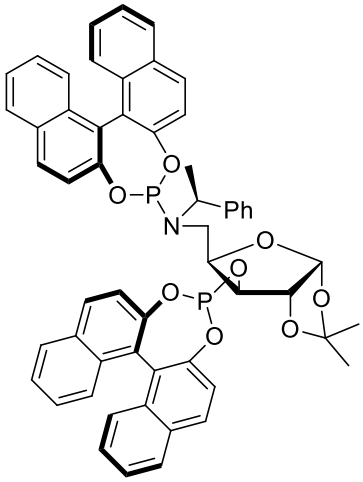
HRMS (ESI) calculated for $C_{64}H_{73}NO_8P_2K$ 1084.4443, found 1084.44515.

$^{31}P\{^1H\}$ NMR (121 MHz, C_6D_6): δ (ppm) = 126.7 (s), 138.2 (s).

^1H NMR (300 MHz, C_6D_6): δ (ppm) = 1.03-1.06 (m, 6H, $C(CH_3)_2$ and $CHCH_3$), 1.23 (s, 9H, $C(CH_3)_3$), 1.26 (s, 3H, $C(CH_3)_2$), 1.29 (s, 18H, $2C(CH_3)_3$), 1.43 (s, 9H, $C(CH_3)_3$), 2.45 (ddd, 1H, H_A-5, $^2J_{5A\text{-}5B}$ = 14.1 Hz, *J* = 6.1 Hz, *J* = 1.8 Hz), 2.67-2.71 (m, 1H, H_B-5, $^2J_{5A\text{-}5B}$ = 14.1 Hz), 3.23-3.32 (m, 1H, $CHCH_3$), 3.70-3.72 (m, 1H, H-3), 4.38 (brs, 1H, H-4), 4.44 (d, 1H, H-2, $^3J_{1\text{-}2}$ = 3.7 Hz), 5.87 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.7 Hz), 6.83-6.88 (m, 1H, CH-Ar), 6.98-7.11 (m, 7H, CH-Ar), 7.28-7.80 (m, 13H, CH-Ar).

^{13}C NMR (125 MHz, C_6D_6): δ (ppm) = 21.9 (d, $CHCH_3$, $J_{C\text{-}P}$ = 19.1 Hz), 26.3 ($C(CH_3)_2$), 26.9 ($C(CH_3)_2$), 31.3 (d, $C(CH_3)_3$, $J_{C\text{-}P}$ = 2.7 Hz), 31.5 (d, $C(CH_3)_3$, $J_{C\text{-}P}$ = 1.1 Hz), 31.6 ($C(CH_3)_3$), 31.6 ($C(CH_3)_3$), 34.6 ($C(CH_3)_3$), 34.7 ($C(CH_3)_3$), 35.5 ($C(CH_3)_3$), 35.6 ($C(CH_3)_3$), 39.5 (C-5), 58.5 (d, $CHCH_3$, $J_{C\text{-}P}$ = 28.8 Hz), 72.2 (d, C-3, $J_{3\text{-}P}$ = 3.4 Hz), 73.6 (C-4), 85.3 (d, C-2, $J_{2\text{-}P}$ = 3.8 Hz), 105.4 (C-1), 111.4 ($C(CH_3)_2$), 120.3 (d, CH_{Ar}, $J_{C\text{-}P}$ = 14.1 Hz), 122.1 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.6 Hz), 122.8 (d, CH_{Ar}, $J_{C\text{-}P}$ = 8.4 Hz), , 124.5 ($2CH_{Ar}$), 124.5 (CH_{Ar}), 124.8 (d, C_{Ar}, $J_{C\text{-}P}$ = 3.1 Hz), 125.2 (CH_{Ar}), 126.7 (CH_{Ar}), 126.8 (CH_{Ar}), 127.0 (CH_{Ar}), 127.0 (CH_{Ar}), 127.1 (CH_{Ar}), 127.1 (CH_{Ar}), 127.1 (CH_{Ar}), 127.4 ($2CH_{Ar}$), 128.2 (CH_{Ar}), 128.3 (CH_{Ar}), 128.4 ($2CH_{Ar}$), 129.3 (CH_{Ar}), 130.2 (CH_{Ar}), 130.7 (C_{Ar}), 131.4 (C_{Ar}), 133.8 (d, C_{Ar}, $J_{C\text{-}P}$ = 3.8 Hz), 133.8 (d, C_{Ar}, $J_{C\text{-}P}$ = 4.4 Hz), 134.7 (C_{Ar}), 135.2 (C_{Ar}), 140.9 (C_{Ar}), 141.0 (C_{Ar}), 143.6 (d, C_{Ar}, $J_{C\text{-}P}$ = 6.6 Hz), 146.1 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 6.6 Hz), 146.3 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 6.3 Hz), 146.9 (d, $2C_{Ar}$, $J_{C\text{-}P}$ = 4.7 Hz), 148.4 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 1.3 Hz), 150.8 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 5.7 Hz).

3-(*R*)-[(1,1'-binaphthyl-2,2'-diyl)phosphite]-5-(*S*)-[(1,1'-binaphthyl-2,2'-diyl)phosphite]-5-deoxy-5-*N*-α-methyl-benzylamino-1,2-*O*-isopropylidene-α-D-xylofuranose (**28i**)



Starting from (*R*)-BINOL (158 mg, 0.55 mmol), (*S*)-BINOL (158 mg, 0.55 mmol), 5-Deoxy-5-*N*-(*S*)-α-methylbenzylamino-1,2-*O*-isopropylidene-α-D-xylofuranose **27e** (147 mg, 0.5 mmol), pyridine (182 mg, 2.3 mmol) and Et_3N (202 mg, 2.0 mmol) in toluene (5 mL), the product **28i** was isolated as a white solid (97 mg, 21 %, R_f 0.28).

$[\alpha]_D^{26}$ = -49.6 (*c* 0.28, $CHCl_3$).

Anal. calcd for $C_{56}H_{45}NO_8P_2$: C, 72.96; H, 4.92; N, 1.52. Found: C, 72.54; H, 5.21; N, 1.28 %.

HRMS (ESI) calculated for $C_{56}H_{46}NO_8P_2$ 922.26932, found 922.26866.

HRMS (ESI) calculated for $C_{56}H_{45}NO_8P_2Na$ 944.25126, found 944.2506.

HRMS (ESI) calculated for $C_{56}H_{45}NO_8P_2K$ 960.22520, found 960.22543.

$^{31}P\{^1H\}$ NMR (121 MHz, C_6D_6): δ (ppm) = 133.1 (s), 145.8 (s).

^1H NMR (300 MHz, C_6D_6): δ (ppm) = 1.06 (s, 3H, $C(CH_3)_2$), 1.36 (s, 3H, $C(CH_3)_2$), 1.88 (dd, 3H, $CHCH_3$, $^3J_{H\text{-}H}$ = 7.2 Hz, $^4J_{H\text{-}P}$ = 3.2 Hz), 3.08 (ddd, 1H, H_A-5, $^2J_{5A\text{-}5B}$ = 15.2 Hz, *J* = 7.7 Hz, *J* = 2.2 Hz), 3.74 (m, 1H, H_B-5), 4.31 (dd, 1H, H-3, $^3J_{3\text{-}P}$ = 9.8 Hz, *J* = 2.8 Hz), 4.49-4.53 (m, 2H, H-2 and H-4), 5.07-5.20 (m, 1H, $CHCH_3$), 5.79 (d, 1H, H-1, $^3J_{1\text{-}2}$ = 3.7 Hz), 6.60-7.14 (m, 9H, CH-Ar), 7.18-7.83 (m, 20H, CH-Ar).

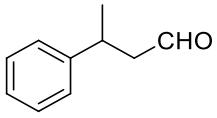
^{13}C NMR (63 MHz, C_6D_6): δ (ppm) = 26.1 ($C(CH_3)_2$), 26.7 ($C(CH_3)_2$), 30.2 ($CHCH_3$), 45.7 (C-5), 59.2 (d, $CHCH_3$, $J_{C\text{-}P}$ = 22.4 Hz), 79.8 (C-3), 83.3 (m, C-4), 84.4 (d, C-2, $J_{2\text{-}P}$ = 1.6 Hz), 105.2 (C-1), 111.7 ($C(CH_3)_2$), 121.8 (CH_{Ar}), 122.0 (d, C_{Ar}), 122.0 (CH_{Ar}), 122.1 (d, CH_{Ar}, $J_{C\text{-}P}$ = 1.7 Hz), 122.4 (d, CH_{Ar}, $J_{C\text{-}P}$ = 1.5 Hz), 122.7 (d, C_{Ar}, $J_{C\text{-}P}$ = 2.0 Hz), 124.8 (CH_{Ar}), 124.9 (d, C_{Ar}), 125.0 (CH_{Ar}), 125.2 (CH_{Ar}), 125.4 (CH_{Ar}), 125.5 (d, C_{Ar}, $J_{C\text{-}P}$ = 5.4 Hz), 126.5 (CH_{Ar}), 126.6 ($2CH_{Ar}$), 126.6 (CH_{Ar}), 127.3 (CH_{Ar}), 127.4 (CH_{Ar}), 127.5 (CH_{Ar}), 127.6 (CH_{Ar}), 127.8 (CH_{Ar}), 128.4 (CH_{Ar}), 128.6 (CH_{Ar}), 128.7 ($2CH_{Ar}$), 128.8 ($2CH_{Ar}$), 128.8 ($2CH_{Ar}$), 130.5 (CH_{Ar}), 130.7 (CH_{Ar}), 130.9 (CH_{Ar}), 131.0 (CH_{Ar}), 131.2 (C_{Ar}), 131.5 (C_{Ar}), 132.0 (C_{Ar}), 132.1 (C_{Ar}), 132.8 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.1 Hz), 133.2 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.1 Hz), 133.3 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.5 Hz), 133.6 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.5 Hz), 144.3 (d, C_{Ar}, $J_{C\text{-}P}$ = 1.3 Hz), 147.3 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 1.2 Hz), 149.4 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 6.8 Hz), 150.3 (C_{Ar}-O), 151.2 (d, C_{Ar}-O, $J_{C\text{-}P}$ = 5.2 Hz).

5.1.2.7 Synthesis of 3-phenylbutanal

General procedure for the asymmetric hydroformylation of α-methyl styrene

The substrate (1.0 eq), $Rh(acac)(CO)_2$ (1 mol%) and the ligand (1.2 mol%) are transferred into a vial, which is placed into a stainless steel autoclave. The solvent (8 mL/1.0 mmol substrate) is added under an argon atmosphere and the autoclave is purged with argon (three times) followed by syngas (three times). The indicated reaction conditions (syngas pressure, temperature and reaction time) are adjusted by an automatic program. After stirring for the adjusted time, the mixture is cooled to room temperature, depressurized and concentrated *in vacuo*. The reaction mixture was analyzed by ^1H NMR. The enantiomeric excess is determined by GC analysis. A racemic mixture of **30**, as sample for the quantitative and qualitative analysis, is prepared by the hydroformylation of α-methyl styrene with 1 mol% $Rh(acac)(CO)_2$ and 5 mol% PPh_3 in toluene.

3-Phenylbutanal (**30**)[151]

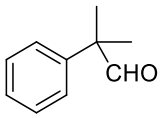


^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.32 (d, 3H, CH_3, $^{3}J_{H\text{-}H}$ = 6.9 Hz), 2.66 (ddd, 1H, H_A-CH, $^{2}J_{A\text{-}B}$ = 16.9 Hz, $^{3}J_{H\text{-}A}$ = 6.9 Hz, $^{3}J_{H\text{-}A}$ = 2.1 Hz), 2.76 (ddd, 1H, H_B-CH_2, $^{3}J_{A\text{-}B}$ = 16.9 Hz, $^{3}J_{H\text{-}B}$ = 6.7 Hz, $^{4}J_{H\text{-}B}$ = 2.0 Hz), 3.36 (m, 1H, CH), 7.15-7.34 (m, 5H, CH-Ar), 9.71 (t, 1H, CHO, $^{3}J_{H\text{-}H}$ = 2.1 Hz).

^{13}C NMR (63 MHz, $CDCl_3$): δ (ppm) = 22.4 (CH_3), 34.5 (CH), 51.9 (CH_2), 126.7 (CH_{Ar}), 127.0 ($2CH_{Ar}$), 128.9 ($2CH_{Ar}$), 145.7 (C_{Ar}), 201.9 (CHO).

Separation of enantiomers by GC on Lipodex E (25 m×0.25 mm), 90/25-6-180; t_R = 13.5 min for (+)-enantiomer and t_R = 13.5 min for (–)-enantiomer.

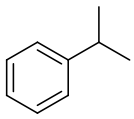
2-Methyl-2-phenylpropanal (**31**)[152]



^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.47 (s, 6H, $2CH_3$), 7.26-7.42 (m, 5H, CH-Ar), 9.51 (s, 1H, CHO).

^{13}C NMR spectrum could not be analyzed due to the small amount in the final reaction mixture.

Cumene[153]



^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.24 (d, 6H, $2CH_3$, $^{3}J_{H\text{-}H}$ = 6.9 Hz), 2.93 (m, 1H, CH), 6.75-7.10 (m, 5H, CH-Ar).

^{13}C NMR spectrum could not be analyzed due to the small amount in the final reaction mixture.

5.2 List of abbreviations

°	Degree(s)
a	Year(s)
α	Specific rotation
Å	Angstrom(s)
Ac	Acetyl
Anal. calcd	Analytical calculated
Ar	Aromatic *or* aryl
asym.	Asymmetric
b/*l*	*Branched* to *linear*
β_n	Natural *bite angle*
eq	Equivalent
BASF	Badische Anilin und Sodafabrik
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
br	Broad
Bu	Butyl
n-BuLi	*normal*-Butyl lithium
c	Concentration
C	Carbon
°C	Degree Celsius
cat.	Catalyst
*c*Hex	Cyclohexyl
conv.	Conversion
D	Spectrum line of sodium at 589 nm *or* deuterium
d	Double *or* doublet *or* deuterated
δ	Chemical shift
Da	Dalton
DABCO	1,4-Diazabicyclo[2.2.2]octane
DCM	Dichloromethane
DEPT	Distortionless enhancement by polarization transfer
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
ea	Equatorial-apical
ee	Equatorial-equatorial *or* enantiomeric excess
e.g.	exempli gratia (for example)
EI	Electron ionization
ESI	Electrospray ionization
Et	Ethyl
et al.	*et alii* (and others)
Et_3N	Triethylamine
EtOAc	Ethyl acetate
Et_2O	Diethyl ether
eV	Electronvolt
f	Frequency
g	Gram(s) *or* gaseous
GC	Gas chromatography
h	Hour(s)
H	Hydrogen *or* proton
HPLC	High pressure liquid chromatography
HP-NMR	High pressure NMR
HRMS	High resolution mass spectrometry
Hünig's base	*N*,*N*-Diisopropylethylamine
Hz	Hertz
i	*iso*

*i*Pr	Isopropyl
J	Coupling constant
J	Joule
l	Length
L	Liter(s)
λ	Wavelength
LDA	Lithium diisopropylamide
m	Meter(s) *or* multiplet
M	Metal
$[M]^+$	Molpeak
m/*z*	*Mass* to *charge*
min	Minute(s)
Me	Methyl
MeCN	Acetonitrile
mol	Mole(s)
mp	Melting point
MS	Mass spectrometry
MTBE	Methyl *tert*-butyl ether
n	*normal*
n.d.	Not determined
Naph	Naphthyl
NMP	*N*-Methyl-2-pyrrolidone
NMR	Nuclear magnetic resonance
OTf	Triflate (trifluoromethanesulfonate)
p	Pressure
Pa	Pascal
PC	Propylene carbonate
pH	Pondus hydrogenii
Ph	Phenyl
ppm	Part(s) per million
R	Organic rest
rac	Racemic
R_f	Response factor
r.t.	Room temperature
s	Singlet
S	Solvent *or* substrate
θ	Tolman's *cone angle*
t	Ton(s)
t	*tert or* time
*t*Bu	*tert*-Butyl
T	Temperature
THF	Tetrahydrofuran
TMS	Trimethylsilyl *or* tetramethylsilane
TOF	Turnover frequency *or* time of flight
TON	Turnover number
q	Quartet
v	Volume
vs.	*versus*

acac	Acetyl acetonato
Alkanox® 240	Tris(2,4-di-*tert*-butylphenyl)phosphite
(*S*,*S*)-BDPP	(2*S*,4*S*)-(+)-2,4-Bis(diphenylphosphino)pentane
(*S*,*S*)-BenzP*	(*S*,*S*)-(–)-1,2-Bis(*tert*-butylmethylphosphino)benzene
(*R*,*R*)-BenzP*	(*R*,*R*)-(+)-1,2-Bis(*tert*-butylmethylphosphino)benzene
(*S*)-BINAP	(*S*)-(–)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene
(*R*)-BINAP	(*R*)-(+)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene
(*R*)-4-Tol-BINAP	(*R*)-(+)-2,2'-Bis(di-*p*-tolylphosphino)-1,1'-binaphthalene
(*R*,*S*)-BINAPHOS	(11b*S*)-4-{[(*R*)-2'-(Diphenylphosphino)-[1,1'-binaphthalen]-2-yl]oxy}dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxophosphepin
(*R*,*R*)-BINAPHOS	(11b*R*)-4-{[(*R*)-2'-(Diphenylphosphino)-[1,1'-binaphthalen]-2-yl]oxy}dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxophosphepin
(*S*)-BINOL	(*S*)-(–)-1,1'-Binaphthalene-2,2'-diol
(*R*)-BINOL	(*R*)-(+)-1,1'-Binaphthalene-2,2'-diol
(*S*)-BIPHEN-H_2	(*S*)-5,5',6,6'-Tetramethyl-3,3'-di-*tert*-butyl-1,1'-biphenyl-2,2'-diol
(*R*)-BIPHEN-H_2	(*R*)-5,5',6,6'-Tetramethyl-3,3'-di-*tert*-butyl-1,1'-biphenyl-2,2'-diol
(*R*)-MeO-BIPHEP	(*R*)-(+)-2,2'-Bis(diphenylphosphino)-6,6'-dimethoxy-1,1'-biphenyl
BiPhePhos	6,6'-[(3,3'-Di-*tert*-butyl-5,5'-dimethoxy-1,1'-biphenyl-2,2'-diyl)bis(oxy)]bis(dibenzo[*d*,*f*][1,3,2]dioxaphosphepin)
BISBI	2,2'-Bis[(diphenylphosphino)methyl]-1,1'-biphenyl
bisDBP	3,3',5,5'-Tetra-*tert*-butyl-1,1'-biphenyl-2,2'-diol
(*S*,*S*,*S*)-BisDiazaPhos	2,2',2",2'"-(1,2-Phenylenebis[(1*S*,3*S*)-tetrahydro-5,8-dioxo-1*H*-[1,2,4]diazaphopholo[1,2-*a*]pyridazine-2,1,3(3*H*)-triyl])tetrakis(*N*-[(1*S*)-1-phenylethyl])benzamide
(*R*,*R*,*S*)-BisDiazaPhos	2,2',2",2'"-(1,2-Phenylenebis[(1*R*,3*R*)-tetrahydro-5,8-dioxo-1*H*-[1,2,4]diazaphopholo[1,2-*a*]pyridazine-2,1,3(3*H*)-triyl])tetrakis(*N*-[(1*S*)-1-phenylethyl])benzamide
(S_{ax},*S*,*S*)-BobPhos	(11a*S*)-4,8-Di-*tert*-butyl-6-{[(2*S*,5*S*)-2,5-diphenylphospholan-1-yl]methoxy}-1,2,10,11-tetramethyldibenzo[*d*,*f*][1,3,2]dioxophosphepin
(*S*,*S*)-Me-BPE	(–)-1,2-Bis[(2*S*,5*S*)-2,5-dimethylphospholano]ethane
(*S*,*S*)-Et-BPE	(–)-1,2-Bis[(2*S*,5*S*)-2,5-dimethylphospholano]ethane
(*S*,*S*)-Ph-BPE	(+)-1,2-Bis[(2*S*,5*S*)-2,5-diphenylphospholano]ethane
(*R*,*R*)-Ph-BPE	(–)-1,2-Bis[(2*R*,5*R*)-2,5-diphenylphospholano]ethane
(–)-BPPM	(2*S*,4*S*)-*N*-(*tert*-Butoxycarbonyl)-4-(diphenylphosphino)-2-[(diphenylphosphino)methyl]pyrrolidine
cat*AS*ium®MQF(*R*)	(–)-1,2-Bis[(2*R*,5*R*)-2,5-dimethylphospholanyl]-3,3,4,4-tetrafluoro-1-cyclobutene
(*S*,*S*)-Chiraphite	(–)-6,6'-{[(1*S*,3*S*)-1,3-Dimethyl-1,3-propanedyl]bis(oxy)}bis[4,8-bis(*tert*-butyl)-2,10-dimethoxy-bibenzo[*d*,*f*][1,3,2]dioxaphosphepin
(*R*,*R*)-Chiraphite	(+)-6,6'-{[(1*R*,3*R*)-1,3-Dimethyl-1,3-propanedyl]bis(oxy)}bis[4,8-bis(*tert*-butyl)-2,10-dimethoxy-bibenzo[*d*,*f*][1,3,2]dioxaphosphepin
(*S*,*S*)-ChiraPhos	(2*S*,4*S*)-(–)-2,4-Bis(diphenylphosphino)butane
cod	1,5-Cyclooctadiene
Crabtree's catalyst	(1,5-Cyclooctadiene)(pyridine)(tricyclohexylphosphine)-iridium(I) hexafluorophosphate
(*R*)-DifluorPhos	(*R*)-(–)-5,5'-Bis(diphenylphosphino)-2,2,2',2'-tetrafluoro-4,4'-bi-1,3-benzodioxole
(*S*,*S*)-DIOP	(4*S*,5*S*)-(+)-4,5-Bis(diphenylphosphinomethyl)-2,2-dimethyl-1,3-dioxolane
(*R*,*R*)-DIPAMP	(*R*,*R*)-(–)-1,2-Bis[(2-methoxyphenyl)(phenylphosphino)]ethane
dppb	1,4-Bis(diphenylphosphino)butane
dppe	1,4-Bis(diphenylphosphino)ethane
dppf	1,1'-Bis(diphenylphosphino)ferrocene
(*R*,*S*)-dppf'bp = (*R*,*S*)-JosiPhos-**4**	(*R*)-1-[(*S*)-2-(Diphenylphosphino)ferrocenyl]ethyldi-*tert*-butylphosphine

(*R*,*R*,*S*,*S*)-DuanPhos	(1*R*,1'*R*,2*S*,2'*S*)-2,2'-Di-*tert*-butyl-2,3',2,3'-tetrahydro,1*H*,1'*H*-(1,1')biisophosphindolyl
(*S*,*S*)-Me-DuPhos	(+)-1,2-Bis[(2*S*,5*S*)-2,5-dimethylphospholano]benzene
(*R*,*R*)-Me-DuPhos	(–)-1,2-Bis[(2*R*,5*R*)-2,5-dimethylphospholano]benzene
(*S*,*S*)-Et-DuPhos	(+)-1,2-Bis[(2*S*,5*S*)-2,5-diethylphospholano]benzene
(*S*,*S*)-*i*Pr-DuPhos	(–)-1,2-Bis[(2*S*,5*S*)-2,5-diisopropylphospholano]benzene
(*S*,*S*)-Et-FerroTANE®	(–)-1,1'-Bis[(2*S*,4*S*)-2,4-diethylphosphotano]ferocene
(*S*,*R*)-JosiPhos	(*S*)-1-[(*R*)-2-(Diphenylphosphino)ferrocenyl]ethyldicyclohexylphosphine
(*R*,*S*)-JosiPhos	(*R*)-1-[(*S*)-2-(Diphenylphosphino)ferrocenyl]ethyldicyclohexylphosphine
(*R*,*S*)-JosiPhos-**1**	(*R*)-1-[(*S*)-2-(Dicyclohexylphosphino)ferrocenyl]ethyldi-*tert*-butylphosphine
(*R*,*S*)-JosiPhos-**2**	(*R*)-1-[(*S*)-2-(Dicyclohexylphosphino)ferrocenyl]ethyldicyclohexylphosphine
(*R*,*S*)-JosiPhos-**3**	(*R*)-1-{(*S*)-2-[Bis(4-methoxy-3,5-dimethylphenyl)phosphino]ferrocenyl}ethyldi(3,5-xylyl)phosphine
(*S*,*R*)-JosiPhos-**4**	(*S*)-1-[(*R*)-2-(Diphenylphosphino)ferrocenyl]ethyldi-*tert*-butylphosphine
(*S*,*S*)-Kelliphite	(*S*,*S*)-(+)-6,6'-[(1,1'-Biphenyl-2,2'-diyl)bis(oxy)]bis[4,8-di-*tert*-butyl-1,2,10,11-tetramethyl]dibenzo[*d*,*f*][1,3,2]dioxaphosphepin
(*R*,*R*)-Kelliphite	(*R*,*R*)-(–)-6,6'-[(1,1'-Biphenyl-2,2'-diyl)bis(oxy)]bis[4,8-di-*tert*-butyl-1,2,10,11-tetramethyl]dibenzo[*d*,*f*][1,3,2]dioxaphosphepin
(*S*,*S*,*R*)-MandyPhos-**1**	(*S*,*S*')-1,1'-Bis(dicyclohexylphosphino)-2,2'-bis[(*R*)-α-(dimethylamino)benzyl]ferrocene
(*S*,*S*,*R*)-MandyPhos-**2**	(*S*,*S*')-1,1'-Bis[(*R*)-α-(dimethylamino)benzyl]-2,2'-bis[diphenylphosphino)ferrocene
(*R*,*R*)-QuinoxP*	(*R*,*R*)-(–)-2,3-Bis(*tert*-butylmethylphosphino)quinoxaline
(*R*)-DTBM-SegPhos	(*R*)-(–)-5,5'-Bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4'-bi-1,3-benzodioxole
(*R*)-SynPhos	(*R*)-(+)-6,6'-Bis(diphenylphosphino)-2,2',3,3'-tetrahydro-5,5'-bi-1,4-benzodioxin
(*S*,*S*,*R*,*R*)-TangPhos	(1*S*,1'*S*,2*R*,2'*R*)-1,1'-Di-*tert*-butyl-(2,2')-diphospholane
(*S*,*S*)- *c*Hex$_2$PThrePHOX	{Dibenzyl[(4*S*,5*S*)-5-methyl-2-phenyl-4,5-dihydro-4-oxazolyl]methyl}dicyclohexylphosphinite
(*S*,*S*)-Ph$_2$PThrePHOX	{Dibenzyl[(4*S*,5*S*)-5-methyl-2-phenyl-4,5-dihydro-4-oxazolyl]methyl}diphenylphosphinite
(*R*)-C$_3$-TunePhos	(*R*)-1,13-Bis(diphenylphosphino)-7,8-dihydro-6*H*-dibenzo[*f*,*h*][1,5]dioxonin
(*R*,*R*)-WalPhos-**1**	(*R*)-1-{(*R*)-2-[2-(Diphenylphosphino)phenyl]ferrocenyl}ethylbis[3,5-bis-(trifluoromethyl)phenyl]phosphine
XantPhos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
(*R*,*S*)-XyliPhos	(*R*)-1-{[(*S*)-2-Diphenylphosphino]ferrocenyl}ethylbis(3,5-dimethylphenyl)phosphine
(*R*,*S*)-YanPhos	(11b*S*)-*N*-[(*R*)-2'-(Diphenylphosphino)-[1,1'-binaphthalen]-2-yl]-*N*-ethyldinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-amine
L1b	3,5-Bis[(3,3'-di-*tert*-butyl-5,5'-dimethoxy-1,1'-biphenyl-2,2'-diyl)phosphite]-1,2-*O*-isopropylidene-α-D-ribofuranose
L2b	3,5-Bis[(3,3'-di-*tert*-butyl-5,5'-dimethoxy-1,1'-biphenyl-2,2'-diyl)phosphite]-1,2-*O*-isopropylidene-α-D-allofuranose
L2c	3,5-Bis[(3,3',5,5'-tetra-*tert*-butyl-1,1'-biphenyl-2,2'-diyl)phosphite]-1,2-*O*-isopropylidene-α-D-allofuranose
L2d	3,5-Bis[(3,3'-bistrimethylsilyl-1,1'-biphenyl-2,2'-diyl)phosphite]-6-deoxy-1,2-*O*-isopropylidene-α-D-allofuranose
L2e	3,5-Bis{[(*S*)-1,1'-binaphthyl-2,2'-diyl]phosphite}-6-deoxy-1,2-*O*-isopropylidene-α-D-allofuranose

L2f	3,5-Bis{[(*R*)-1,1'-binaphthyl-2,2'-diyl]phosphite}-6-deoxy-1,2-*O*-isopropylidene-α-D-allofuranose
L3c	3,5-Bis[(3,3',5,5'-tetra-*tert*-butyl-1,1'-biphenyl-2,2'-diyl)phosphite]-3-amine-3-deoxy-1,2-*O*-isopropylidene-α-D-ribofuranose
L4c	3,5-Bis[(3,3',5,5'-tetra-*tert*-butyl-1,1'-biphenyl-2,2'-diyl)phosphite]-3-amine-3-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose
L5c	3,5-Bis[(3,3',5,5'-tetra-*tert*-butyl-1,1'-biphenyl-2,2'-diyl)phosphite]-5-amine-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose
L6a	3,5-Bis[(1,1'-biphenyl-2,2'-diyl)phosphite]-1,2-*O*-isopropylidene-α-D-xylofuranose
L6b	3,5-Bis[(3,3'-di-*tert*-butyl-5,5'-dimethoxy-1,1'-biphenyl-2,2'-diyl)phosphite]-1,2-*O*-isopropylidene-α-D-xylofuranose
L6c	3,5-Bis[(3,3',5,5'-tetra-*tert*-butyl-1,1'-biphenyl-2,2'-diyl)phosphite]-1,2-*O*-isopropylidene-α-D-xylofuranose
L6e	3,5-Bis{[(*S*)-1,1'-binaphthyl-2,2'-diyl]phosphite}-1,2-*O*-isopropylidene-α-D-xylofuranose
L6f	3,5-Bis{[(*R*)-1,1'-binaphthyl-2,2'-diyl]phosphite}-1,2-*O*-isopropylidene-α-D-xylofuranose
L6g	3,5-Bis{[(*S*)-3,3'-bistrimethylsilyl-1,1'-binaphthyl-2,2'-diyl]phosphite}-1,2-*O*-isopropylidene-α-D-xylofuranose
L6h	3,5-Bis{[(*R*)-3,3'-bistrimethylsilyl-1,1'-binaphthyl-2,2'-diyl]phosphite}-1,2-*O*-isopropylidene-α-D-xylofuranose
L7b	3,5-Bis[(3,3'-di-*tert*-butyl-5,5'-dimethoxy-1,1'-biphenyl-2,2'-diyl)phosphite]-6-deoxy-1,2-*O*-isopropylidene-β-L-idofuranose
L7c	3,5-Bis[(3,3',5,5'-tetra-*tert*-butyl-1,1'-biphenyl-2,2'-diyl)phosphite]-6-deoxy-1,2-*O*-isopropylidene-β-L-idofuranose
L8d	3,5-Bis[(3,3'-bistrimethylsilyl-1,1'-biphenyl-2,2'-diyl)phosphite]-6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose
L8e	3,5-Bis{[(*S*)-1,1'-binaphthyl-2,2'-diyl]phosphite}-6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose
L8f	3,5-Bis{[(*R*)-1,1'-binaphthyl-2,2'-diyl]phosphite}-6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose
L8g	3,5-Bis{[(*S*)-3,3'-bistrimethylsilyl-1,1'-binaphthyl-2,2'-diyl]phosphite}-6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose
A	1,2-Bis[(4*R*,5*S*,6*S*,7*R*)-5,6-dimethoxy-4,7-dimethyl-1,3,2-dioxophosphepan-2-yl)ethane
B	(*S*)-1,4-Bis(diphenylphosphino)butan-2-amine
C	{(*S*)-2-[2-((*R*,*R*)-2,5-Dimethylphospholan-1-yl)phenyl]-4-isopropyl-4,5-dihydrooxazole}(1,5-cyclooctadiene)iridium(I) hexafluorophosphate
D	Dichloro[(*R*)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl][(*R*,*R*)-1,2-diphenylethane diamine]ruthenium(II)
E	Dichloro[(*S*)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl][(*S*,*S*)-1,2-diphenylethane diamine]ruthenium(II)
F	Dichloro[(*S*)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl][(*R*,*R*)-1,2-diphenylethane diamine]ruthenium(II)
G	(1*S*,1'*S*)-(9,9-Dimethyl-9*H*-xanthene-4,5-diyl)bis[phenyl(*o*-tolyl)phosphine]
H	(1*S*,1'*S*)-(9,9-Dimethyl-9*H*-xanthene-4,5-diyl)bis[(2-methoxyphenyl)(phenyl) phosphine]
I	(1*S*,1'*S*)-(9,9-Dimethyl-9*H*-xanthene-4,5-diyl)bis(naphthalen-2-yl(phenyl)phosphine]

5.3 Applied ligands in this dissertation

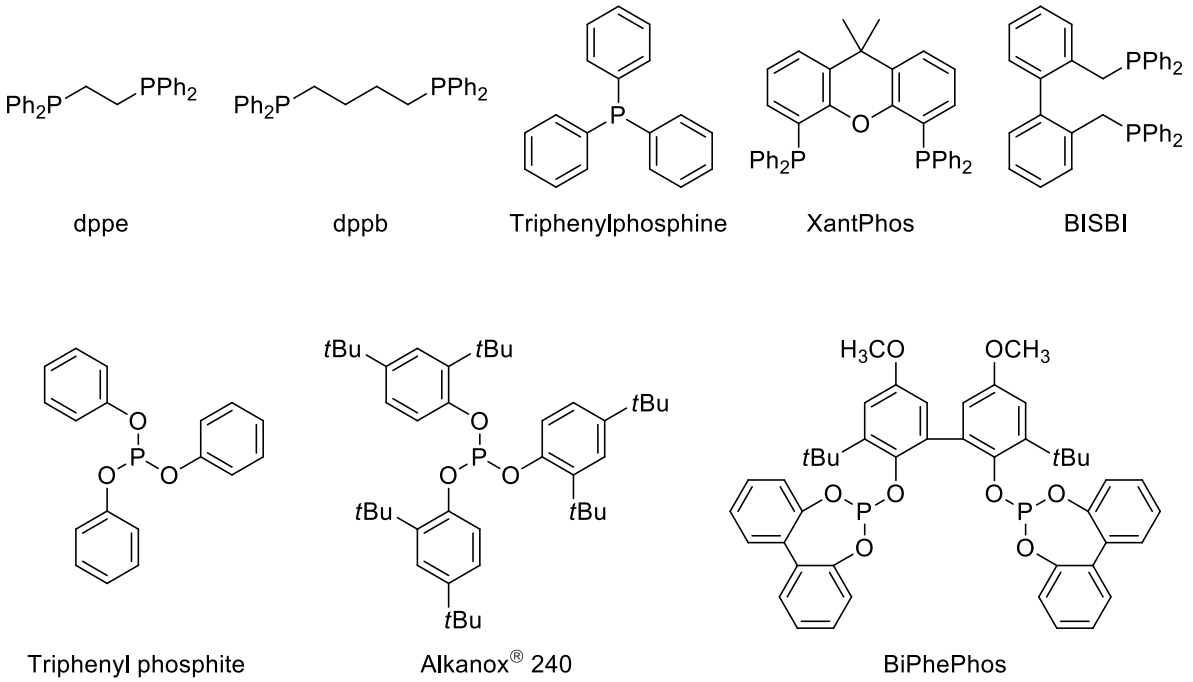
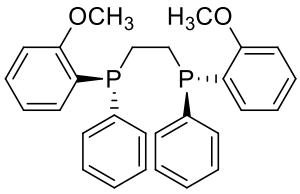
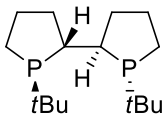


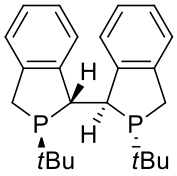
Figure 24. Applied achiral ligands in this dissertation.



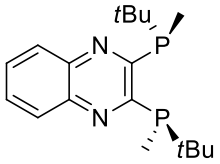
(*R*,*R*)-DiPAMP



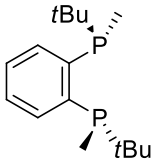
(*S*,*S*,*R*,*R*)-TangPhos



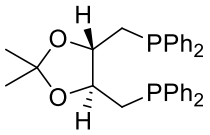
(*R*,*R*,*S*,*S*)-DuanPhos



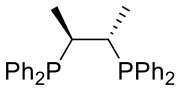
(*R*,*R*)-QuinoxP*



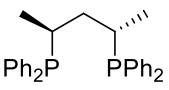
(*S*,*S*)-BenzP*



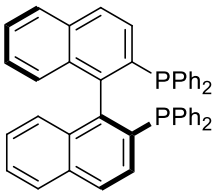
(*S*,*S*)-DIOP



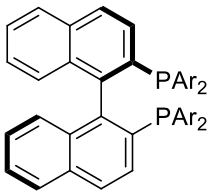
(*S*,*S*)-ChiraPhos



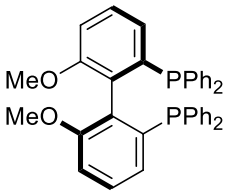
(*S*,*S*)-BDPP



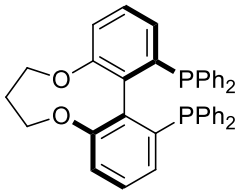
(*S*)-BINAP



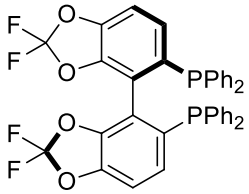
(*R*)-BINAP Ar = Ph
(*R*)-4-Tol-BINAP Ar = 4-Tol



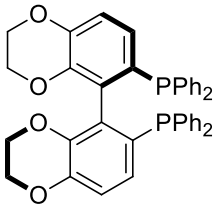
(*R*)-MeO-BIPHEP



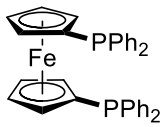
(*R*)-C_3-TunePhos



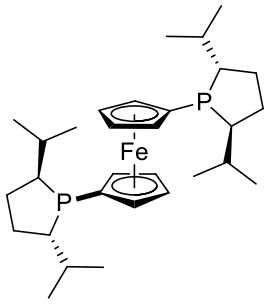
(*R*)-DifluorPhos



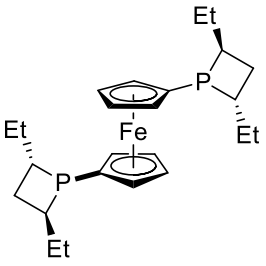
(*R*)-SynPhos



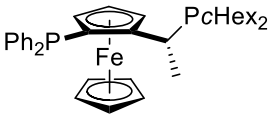
dppf



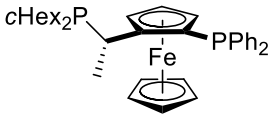
1,1'-Bis[(2*R*,5*R*)-2,5-di-isopropylphospholano]ferrocene



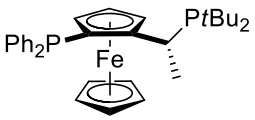
(*S*,*S*)-Et-FerroTANE®



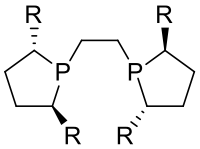
(*R*,*S*)-JosiPhos



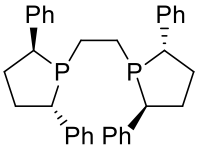
(*S*,*R*)-JosiPhos



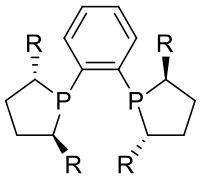
(*R*,*S*)-dppf^{t}bp



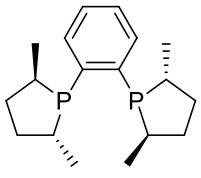
(*S*,*S*)-Me-BPE R = Me
(*S*,*S*)-Et-BPE R = Et



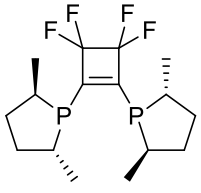
(*R*,*R*)-Ph-BPE



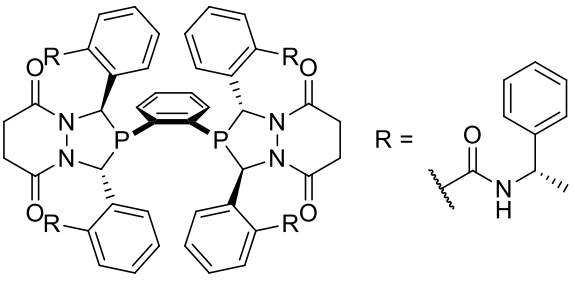
(*S*,*S*)-Me-DuPhos R = Me
(*S*,*S*)-Et-DuPhos R = Et
(*S*,*S*)-*i*Pr-DuPhos R = *i*Pr



(*R*,*R*)-Me-DuPhos



cat*A*Sium®MQF(*R*)



(*R*,*R*,*S*)-BisDiazaPhos

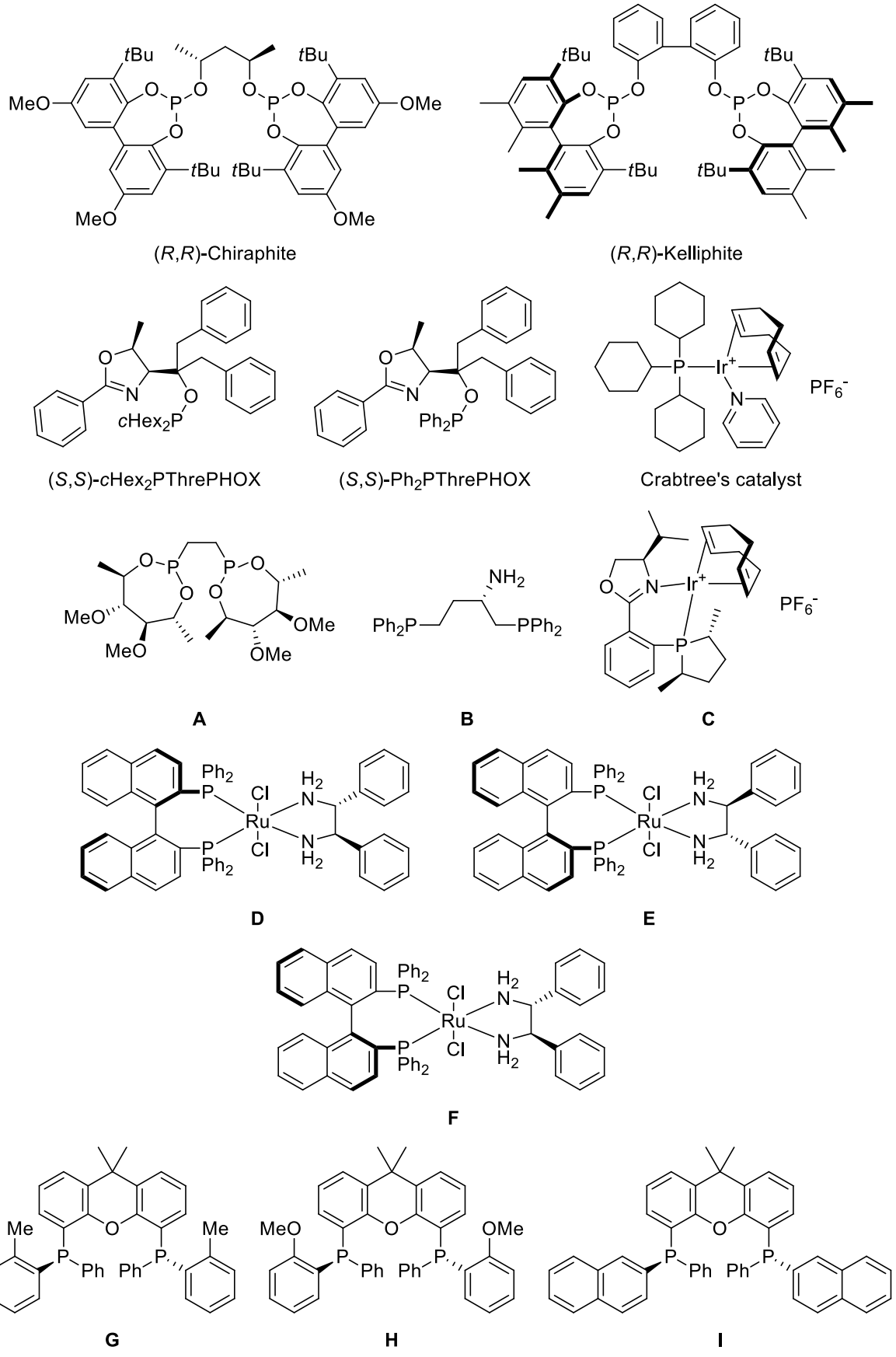


Figure 25. Applied ligands in this dissertation.

5.4 Supplementary information

Table 34. Asymmetric hydrogenation of **1a** with different catalysts in THF.[a]

Entry	Catalyst	Yield[b] [%]	ee[c] [%]
1[d]	**C**[e]	31	1 (*S*)
2	**D**[e]	16	4 (*S*)
3	**E**[e]	6	2 (*R*)
4	**F**[e]	6	9 (*S*)
5	Ir((*S*,*S*)-Ph_2PThrePHOX)(cod)	69	4 (*R*)
6	Ir((*S*,*S*)-*c*Hex_2PThrePHOX)(cod)	67	4 (*S*)

[a] 1.0 mmol of **1a**, catalyst 10.0 µmol, H_2, 4 mL of THF, 50 °C, 5.0 MPa, S/Rh = 100, 20 h.
[b] Yields were determined by ^{1}H NMR spectroscopy.
[c] Ee-values were determined by GC analysis; absolute configurations were compared to synthesized enantiomerically pure *O*-silylated methyl lactate.
[d] Reaction was performed at 40 °C and 1.5 MPa.
[e] Catalysts **C-F** were recently prepared in the research group of Prof. Börner and shown in Chapter 5.3.

Table 35. Rh-catalyzed asymmetric hydroformylation of **6a** with non-commercial and new ligands.[a]

Entry	Ligand	Conv.[b] [%]	14[b] [%]	15[b,c] [%]	8a[b] [%]	(*E*)-9a[b] [%]	(*Z*)-9a[b] [%]	ee[d] [%]
1	**20f**	100	1	<1	62	10	26	n.d.
2	**21a**	100	30	–	22	24	24	rac
3	**22b**	100	11	–	74	5	10	rac
4	**G**[f]	53	2	<1	32	4	15	n.d.

[a] 0.5 mmol of **6a**, Rh(acac)$(CO)_2$ 5.0 µmol, PP-ligand 6.0 µmol, CO/H_2 = 1:1, 5 mL of toluene, 30 °C, 2.0 MPa, S/Rh = 100, 63 h.
[b] Conversions and yields were determined by ^{1}H NMR spectroscopy.
[c] Due to the small amount in the final mixture, the amount of the linear aldehyde (**15**) was determined by integration of the characteristic signal for the proton of the aldehyde group (δ = 9.39 ppm) in ^{1}H NMR spectroscopy.
[d] Ee-values of the branched aldehyde (**14**) were determined by GC analysis.
[f] Ligand **G** was recently prepared in the research group of Prof. Börner and shown in Chapter 5.3.

Table 36. Rh-catalyzed asymmetric hydroformylation of **16a**.[a]

Entry	Ligand	Conv.[b] [%]	17a[b] [%]	18a[b] [%]	19a[b] [%]	ee[c] [%]
1[d]	(*S*,*S*)-DIOP	64	<1	–	63	n.d.
2[e]	(*S*,*S*)-DIOP	56	48	<1	7	4 (–)
3[f]	(*S*,*S*)-DIOP	50	35	3	11	7 (–)
4	(*S*,*S*)-DIOP/PPh_3 (1:1)	72	52	9	11	8 (–)
5[d]	(*R*,*R*)-QuinoxP*	93	36	2	55	10 (–)
6[g]	(*R*,*R*)-QuinoxP*	64	21	8	34	16 (–)
7[h]	(*R*,*R*)-QuinoxP*	17	1	2	14	23 (–)
8[d]	(*S*,*S*)-BenzP*	68	34	4	29	2 (+)
9	(*S*,*S*)-ChiraPhos	42	21	3	18	24 (+)
10	**21a**	>99	97	<1	3	15 (–)
11[g]	**21a**	67	64	1	2	19 (–)
12[h,i]	**21a**	12	9	3	<1	14 (–)
13[e]	**21a**	62	59	1	2	12 (–)
14[k]	**21a**	39	37	1	1	22 (–)
15[l]	**21a**	79	75	1	3	11 (–)
16[m]	**21a**	66	62	<1	4	3 (–)
17	**21b**	>99	94	<1	6	6 (–)
18[g]	**21b**	85	80	2	3	8 (–)
19	**21c**	69	64	<1	5	14 (–)
20[g]	**21c**	13	12	<1	<1	19 (–)
21	**21d**	66	63	<1	2	10 (–)
22[g]	**21d**	16	14	<1	<1	10 (–)
23[g]	**21e**	32	30	<1	1	3 (–)
24	**G**[n]	65	59	1	5	11 (+)
25[g]	**G**[n]	45	40	2	2	28 (+)
26[h,o]	**G**[n]	46	37	6	3	41 (+)
27[g]	**H**[n]	71	62	2	8	4 (–)
28[g]	**I**[n]	89	77	2	10	11 (–)

[a] 0.5 mmol of **16a**, $Rh(acac)(CO)_2$ 5.0 µmol, PP-ligand 6.0 µmol, CO/H_2 = 1:1, 5 mL of toluene, 100 °C, 1.0 MPa, S/Rh = 100, 21 h.
[b] Conversions and yields were determined by ^{31}P NMR spectroscopy.
[c] Ee-values of the linear aldehyde (**17a**) were determined by GC analysis.
[d] Reaction was performed with a partial pressure ratio CO/H_2 = 1:5.
[e] Reaction was performed in THF.
[f] Reaction was performed with $[Rh(cod)_2]BF_4$.
[g] Reaction was performed at 80 °C.
[h] Reaction was performed at 60 °C.
[i] Reaction was performed under 3.0 MPa.
[k] Reaction was performed in DCM.
[l] Reaction was performed in EtOAc.
[m] Reaction was performed in heptane.
[n] Ligands **G-I** were recently prepared in the research group of Prof. Börner and shown in Chapter 5.3.
[o] $Rh(acac)(CO)_2$ 25.0 µmol, ligand 30.0 µmol.

5.5 References

[1] Tranter, G. E. *Mol. Phys.* **1985**, *56*, 825-838.

[2] *Catalysis from A to Z - A Concise Encyclopedia*; Cornils, B., Herrmann, W. A., Schlögl, R., Wong, C.-H., Eds; WILEY-VCH: Weinheim, 2003.

[3] *Angewandte homogene Katalyse*; Behr, A., Eds; WILEY-VCH: Weinheim, Germany, 2008.

[4] (a) Pfaltz, A.; Blankenstein, J.; Hilgraf, R.; Hörmann, E.; McIntyre, S.; Menges, F.; Schönleber, M.; Smidt, S. P.; Wüstenberg, B.; Zimmermann, N. *Adv. Synth. Catal.* **2003**, *345*, 33-45. (b) Cui, X.; Burgess, K. *Chem. Rev.* **2005**, *105*, 3272-3296. (c) Källström, K.; Munslow, I.; Andersson, P. G. *Chem. Eur. J.* **2006**, *12*, 3194-3200. (d) Roseblade, S. J.; Pfaltz, A. *Acc. Chem. Res.* **2007**, *40*, 1402-1411. (e) Mazuela, J.; Verendel, J. J.; Coll, M.; Schäffner, B.; Börner, A.; Andersson, P. G.; Pàmies, O.; Diéguez, M. *J. Am. Chem. Soc.* **2009**, *131*, 12344-12353.

[5] (a) Kitamura, M.; Tsukamoto, M.; Bessho, Y.; Yoshimura, M.; Kobs, U.; Widhalm, M.; Noyori, R. *J. Am. Chem. Soc.* **2002**, *124*, 6649-6667. (b) Gridnev, I. D.; Imamoto, T. *Acc. Chem. Res.* **2004**, *37*, 633-643.

[6] Koenig, K. E.; Sabacky, M. J.; Bachmann, G. L.; Christopfel, W. C.; Barnstorff, H. D.; Friedman, R. B.; Knowles, W. S.; Stults, B. R.; Vineyard, B. D.; Weinkauff, D. J. *Ann. N.Y. Acad. Sci.* **1980**, *333*, 16-22.

[7] Blaser, H.-U.; Malan, C.; Pugin, B.; Spindler, F.; Steiner, H.; Studer, M. *Adv. Synth. Catal.* **2003**, *345*, 103-151.

[8] Halpern, J. *Science* **1982**, *217*, 401-406.

[9] (a) *Asymmetric Catalysis on Industrial Scale*; 1st ed.; Blaser, H. U., Federsel, H.-J., Eds; WILEY-VCH: Weinheim, Germany, 2004. (b) *Asymmetric Catalysis on Industrial Scale*; 2nd ed.; Blaser, H.-U., Federsel, H.-J., Eds; WILEY-VCH: Weinheim, Germany, 2010.

[10] Blaser, H. U.; Hanreich, R.; Schneider, H. D.; Spindler, F.; Steinacher, B. In *Asymmetric Catalysis on Industrial Scale*; 1st ed.; Blaser, H. U., Schmidt, S., Eds; WILEY-VCH: Weinheim, Germany, 2004; pp 55-70.

[11] (a) Jäkel, C.; Paciello, R.; BASF SE, Christoph Jaekel, Rocco Paciello; WO2006040096, 2006. (b) Schmidt-Leithoff, J.; Jäkel, C.; Paciello, R.; BASF SE; EP2139835, 2008. (c) Heydrich, G.; Gralla, G.; Rauls, M.; Schmidt-Leithoff, J.; Ebel, K.; Krause, W.; Oehlenschläger, S.; Jäkel, C.; Friedrich, M.; Bergner, E. J.; Kashani-Shirazi, N.; Paciello, R.; BASF; US20100249467, 2009.

[12] (a) Selke, R. In *Asymmetric Catalysis on Industrial Scale*; 1st ed.; Blaser, H. U., Schmidt, S., Eds; WILEY-VCH: Weinheim, Germany, 2004; pp 39-53. (b) Knowles, W. S. In *Asymmetric Catalysis on Industrial Scale*; 1st ed.; Blaser, H. U., Schmidt, S., Eds; WILEY-VCH: Weinheim, Germany, 2004; pp 23-38. (c) *Asymmetric Catalysis on Industrial Scale: Challenges, Approaches and Solutions*; Blaser, H.-U., Schmidt, E., Eds; WILEY-VCH: Weinheim, Germany, 2004.

[13] Cornils, B.; Herrmann, W. A.; Rasch, M. *Angew. Chem.* **1994**, *106*, 2219-2238.

[14] *Industrielle organische Chemie*; Arpe, H.-J., Eds; WILEY-VCH: Weinheim, Germany, 2007.

[15] (a) Whiteker, G. T.; Cobley, C. J. *Top. Organomet. Chem.* **2012**, *42*, 35-46. (b) *75 JAHRE OXO-SYNTHESE*; Frey, G., Dämbkes, G., Eds; Klartext: Essen, Germany, 2013.

[16] (a) Osborn, J. A.; Wilkinson, G.; Young, J. F. *Chem. Commun. (London)* **1965**, 17-17. (b) Evans, D.; Osborn, J. A.; Wilkinson, G. *J. Chem. Soc.* **1968**, 3133-3142.

[17] (a) Clarke, M. L.; Roff, G. J. *Chem. Eur. J.* **2006**, *12*, 7978-7986. (b) Keulemans, A. I. M.; Kwantes, A.; van Bavel, T. *Recl. Trav. Chim. Pays-Bas* **1948**, *67*, 298-308.

[18] (a) Botteghi, C.; Paganelli, S.; Schionato, A.; Marchetti, M. *Chirality* **1991**, *3*, 355-369. (b) Gladiali, S.; Pinna, L. *Tetrahedron: Asymmetry* **1990**, *1*, 693-696. (c) Gladiali, S.; Pinna, L. *Tetrahedron: Asymmetry* **1991**, *2*, 623-632. (d) Wang, X.; Buchwald, S. L. *J. Org. Chem.* **2013**, *78*, 3429-3433.

[19] Tolman, C. A. *Chem. Rev.* **1977**, *77*, 313-348.

[20] (a) Casey, C. P.; Whiteker, G. T. *Isr. J. Chem.* **1990**, *30*, 299-304. (b) Casey, C. P.; Whiteker, G. T.; Melville, M. G.; Petrovich, L. M.; Gavney Jr, J. A.; Powell, D. R. *J. Am. Chem. Soc.* **1992**, *114*, 5535-5543.

[21] (a) van Leeuwen, P. W.; Kamer, P. C.; Reek, J. N.; Dierkes, P. *Chem. Rev.* **2000**, *100*, 2741-2770. (b) Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Reek, J. N. H. *Acc. Chem. Res.* **2001**, *34*, 895-904.

[22] (a) *Homogenous Catalysis: Understanding the Art*; van Leeuwen, P. W. N. M., Eds; Kluwer Academic: Dordrecht, 2004. (b) *Ferrocenes: Ligands, Materials and Biomolecules*; Stepnicka, P., Eds; WILEY-VCH: Weinheim, Germany, 2008.

[23] van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Reek, J. N. H. *Pure Appl. Chem.* **1999**, *71*, 1443-1452.

[24] (a) Wang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2011**, *133*, 19080-19083. (b) Zheng, X.; Cao, B.; Liu, T.-l.; Zhang, X. *Adv. Synth. Catal.* **2013**, *355*, 679-684.

[25] (a) Klosin, J.; Landis, C. R. *Acc. Chem. Res.* **2007**, *40*, 1251-1259. (b) Gual, A.; Godard, C.; Castillón, S.; Claver, C. *Tetrahedron: Asymmetry* **2010**, *21*, 1135-1146. (c) *Rhodium Catalyzed Hydroformylation*; van Leeuwen, P. W. N. M., Claver, C., Eds; Kluwer Arcademic: Dordrecht, 2002. (d) Agbossou, F.; Carpentier, J.-F.; Montreux, A. *Chem. Rev.* **1995**, *95*, 2485-2506.

[26] (a) Franke, R.; Selent, D.; Börner, A. *Chem. Rev.* **2012**, *112*, 5675-5732. (b) Gusevskaya, E. V.; Jiménez-Pinto, J.; Börner, A. *ChemCatChem* **2014**, *6*, 382-411.

[27] (a) Cobley, C. J.; Gardner, K.; Klosin, J.; Praquin, C.; Hill, C.; Whiteker, G. T.; Zanotti-Gerosa, A.; Petersen, J. L.; Abboud, K. A. *J. Org. Chem.* **2004**, *69*, 4031-4040. (b) Nozaki, K.; Sakai, N.; Nanno, T.; Higashijima, T.; Mano, S.; Horiuchi, T.; Takaya, H.; V, K. U. *J. Am. Chem. Soc.* **1997**, *119*, 4413-4423. (c) Nozaki, K.; Itoi, Y.; Shibahara, F.; Shirakawa, E.; Ohta, T.; Takaya, H.; Hiyama, T. *J. Am. Chem. Soc.* **1998**, *120*, 4051-4052. (d) Cobley, C. J.; Froese, R. D. J.; Klosin, J.; Qin, C.; Whiteker, G. T.; Abboud, K. A.; Uni, V.; Gaines, V. *Organometallics* **2007**, *26*, 2986-2999. (e) Erre, G.; Enthaler, S.; Junge, K.; Gladiali, S.; Beller, M. *J. Mol. Catal. A: Chem.* **2008**, *280*, 148-155. (f) Axtell, A. T.; Klosin, J.; Whiteker, G. T.; Cobley, C. J.; Fox, M. E.; Jackson, M.; Abboud, K. A. *Organometallics* **2009**, *28*, 2993-2999. (g) Robert, T.; Abiri, Z.; Wassenaar, J.; Sandee, A. J.; Romanski, S.; Neudörfl, J. r.-M.; Schmalz, H.-G. n.; Reek, J. N. H. *Organometallics* **2010**, *29*, 478-483. (h) Wassenaar, J.; de Bruin, B.; Reek, J. N. H. *Organometallics* **2010**, *29*, 2767-2776.

[28] (a) McDonald, R. I.; Wong, G. W.; Neupane, R. P.; Stahl, S. S.; Landis, C. R. *J. Am. Chem. Soc.* **2010**, *132*, 14027-14029. (b) Sakai, N.; Nozaki, K.; Takaya, H. *J. Chem. Soc., Chem. Commun.* **1994**, 395-396. (c) Kollár, L.; Farkas, E.; Bâtiu, J. *J. Mol. Catal. A: Chem.* **1997**, *115*, 283-288. (d) Watkins, A. L.; Hashiguchi, B. G.; Landis, C. R. *Org. Lett.* **2008**, *10*, 4553-4556. (e) Mazuela, J.; Coll, M.; Pàmies, O.; Diéguez, M. *J. Org. Chem.* **2009**, *74*, 5440-5445. (f) Worthy, A. D.; Joe, C. L.; Lightburn, T. E.; Tan, K. L. *J. Am. Chem. Soc.* **2010**, *132*, 14757-14759. (g) Chikkali, S. H.; Bellini, R.; Berthon-Gelloz, G.; van der Vlugt, J. I.; de Bruin, B.; Reek, J. N. H. *Chem. Commun. (Camb.)* **2010**, *46*, 1244-1246. (h) Clemens, A. J. L.; Burke, S. D. *J. Org. Chem.* **2012**, *77*, 2983-2985.

[29] (a) Giordano, C.; Villa, M.; Panossian, S. In *Chirality in Industry*; Collins, A. N., Sheldrake, G. N., Crosby, J., Eds; WILEY-VCH: Chichester, U. K., 1992; pp 303-312. (b) Tanaka, R.; Nakano, K.; Nozaki, K. *J. Org. Chem.* **2007**, *72*, 8671-8676.

[30] (a) Jeulin, S.; Ayad, T.; Ratovelomanana-Vidal, V.; Genêt, J.-P. *Adv. Synth. Catal.* **2007**, *349*, 1592-1596. (b) Holz, J.; Schäffner, B.; Zayas, O.; Spannenberg, A.; Börner, A. *Adv. Synth. Catal.* **2008**, *350*, 2533-2543.

[31] Wong, G. W.; Landis, C. R. *Org. Synth.* **2012**, *89*, 243-254.

[32] Lambers-Verstappen, M. M. H.; de Vries, J. G. *Adv. Synth. Catal.* **2003**, *345*, 478-482.

[33] Thomas, P. J.; Axtell, A. T.; Klosin, J.; Peng, W.; Rand, C. L.; Clark, T. P.; Landis, C. R.; Abboud, K. A. *Org. Lett.* **2007**, *9*, 2665-2668.

[34] (a) Consiglio, G.; Morandini, F.; Scalone, M.; Pino, P. *J. Organomet. Chem.* **1985**, *279*, 193-202. (b) Ojima, I.; Takai, M.; Takahashi, T.; Mitsubishi Chemical Corporation, Iwao Ojima, Takayoshi Takahashi, Masaki Takai, Research Foundation for the State University of New York WO2004078766, 2004. (c) Parrinello, G.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 7122-7127. (d) Kollár, L.; Consiglio, G.; Pino, P. *J. Organomet. Chem.* **1987**, *330*, 305-314. (e) Kollár, L.; Bakos, J.; Tóth, I.; Heil, B. *J. Organomet. Chem.* **1988**, *350*, 277-284. (f) Consiglio, G.; Kollár, L.; Kölliker, R. *J. Organomet. Chem.* **1990**, *396*, 375-383. (g) Uhlemann, M.; Börner, A. *ChemCatChem* **2012**, *4*, 753-754. (h) Breit, B. *Angew. Chem. Int. Ed.* **1996**, *35*, 2835-2837. (i) Alper, H.; Zhou, J.-Q. *J. Org. Chem.* **1992**, *57*, 3729-3731. (j) Lee, C. W.; Alper, H. *J. Org. Chem.* **1995**, *60*, 499-503.

[35] Achiwa, K. *J. Am. Chem. Soc.* **1976**, *98*, 8265-8266.

[36] Knowles, W. S.; Sabacky, M. J. *Chem. Commun. (London)* **1968**, 1445-1446.

[37] (a) Knowles, W. S.; Sabacky, M. J.; Vineyard, B. D. *J. Chem. Soc., Chem. Commun.* **1972**, 10-11. (b) Vineyard, B. D.; Knowles, W. S.; Sabacky, M. J.; Bachmann, G. L.; Weinkauff, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 5946-5952.

[38] (a) Fryzuk, M. D.; Bosnich, B. *J. Am. Chem. Soc.* **1977**, *99*, 6262-6267. (b) Dang, T. P.; Kagan, H. B. *Chem. Commun.* **1971**, 481-481.

[39] (a) Trost, B. M.; Vaultier, M.; Santiago, M. L. *J. Am. Chem. Soc.* **1980**, *102*, 7932-7934. (b) Sayo, N.; Zhang, X.; Ohmoto, T.; Yoshida, A.; Yokozawa, T.; Takasago International Corporation; US005693868, 1997.

[40] (a) Schmid, R.; Foricher, J.; Cereghetti, M.; Schönholzer, P. *Helv. Chim. Acta* **1991**, *74*, 370-389. (b) Zhang, Z.; Qian, H.; Longmire, J.; Zhang, X. *J. Org. Chem.* **2000**, *65*, 6223-6226. (c) Duprat de Paule, S.; Jeulin, S.; Ratovelomanana-Vidal, V.; Genêt, J.-P.; Champion, N.; Dellis, P. *Tetrahedron Lett.* **2003**, *44*, 823-826. (d) Jeulin, S.; Duprat de Paule, S.; Ratovelomanana-Vidal, V.; Genêt, J.-P.; Champion, N.; Dellis, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 320-325.

[41] (a) Burk, M. J.; Feaster, J. E.; Harlow, R. L. *Organometallics* **1990**, *9*, 2653-2655. (b) Burk, M. J. *J. Am. Chem. Soc.* **1991**, *113*, 8518-8519.

[42] Holz, J.; Quirmbach, M.; Schmidt, U.; Heller, D.; Stu, R.; Bo, A. *J. Org. Chem.* **1998**, *63*, 8031-8034.

[43] Clark, T. P.; Landis, C. R.; Freed, S. L.; Klosin, J.; Abboud, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 5040-5042.

[44] Imamoto, T.; Nishimura, M.; Koide, A.; Yoshida, K. *J. Org. Chem.* **2007**, *72*, 7413-7416.

[45] Yamamoto, Y.; Koizumi, T.; Katagiri, K.; Furuya, Y.; Danjo, H.; Imamoto, T.; Yamaguchi, K. *Org. Lett.* **2006**, *8*, 6103-6106.

[46] Babin, J. E.; Whiteker, G. T.; Union Carbide; WO1993003839, 1993.

[47] (a) Cobley, C. J.; Klosin, J.; Qin, C.; Whiteker, G. T. *Org. Lett.* **2004**, *6*, 3277-3280. (b) Cobley, C. J.; Klosin, J.; Qin, C.; Whiteker, G. T. *Org. Lett.* **2005**, *7*, 1197-1197.

[48] Sakai, N.; Satoshi, M.; Nozaki, K.; Takaya, H. *J. Am. Chem. Soc.* **1993**, *115*, 7033-7034.

[49] (a) Higashizima, T.; Sakai, N.; Nozaki, K.; Takaya, H. *Tetrahedron Lett.* **1994**, *35*, 2023-2026. (b) Nanno, T.; Sakai, N.; Nozaki, K.; Takaya, H. *Tetrahedron: Asymmetry* **1995**, *6*, 2583-2591. (c) Horiuchi, T.; Ohta, T.; Takaya, H. *Chem. Commun.* **1996**, 155-156.

[50] Yan, Y.; Zhang, X. *J. Am. Chem. Soc.* **2006**, *128*, 7198-7202.

[51] Noonan, G. M.; Fuentes, J. A.; Cobley, C. J.; Clarke, M. L. *Angew. Chem. Int. Ed.* **2012**, *51*, 2477-2480.

[52] Noonan, G. M.; Cobley, C. J.; Mahoney, T.; Clarke, M. L. *Chem. Commun. (Camb.)* **2014**, *50*, 1475-1477.

[53] (a) Tolman, C. A. *J. Am. Chem. Soc.* **1972**, *94*, 2994-2999. (b) Hendrix, W. T.; Rosenberg, J. L. *J. Am. Chem. Soc.* **1976**, *98*, 4850-4852.

[54] Casey, C. P.; Cyr, C. R. *J. Am. Chem. Soc.* **1973**, *95*, 2248-2253.

[55] Inoue, S.-I.; Takaya, H.; Tani, K.; Otsuka, S.; Sato, T.; Noyori, R. *J. Am. Chem. Soc.* **1990**, *112*, 4897-4905.

[56] Christiansen, A.; Börner, A. In *Handbook of CH Transformations*; Dyker, G., Eds; WILEY-VCH: Weinheim, Germany, 2005; pp 430-438.

[57] (a) Garlotta, D. *J. Polym. Environ.* **2002**, *9*, 63-84. (b) Gattin, R.; Copinet, A.; Bertrand, C.; Couturier, Y. *J. Polym. Environ.* **2002**, *9*, 11-17. (c) Numata, K.; Srivastava, R. K.; Finne-Wistrand, A.; Albertsson, A.-C.; Doi, Y.; Abe, H. *Biomacromolecules* **2007**, *8*, 3115-3125.

[58] (a) Ohkuma, T.; Kitamura, M.; Noyori, R. In *Catalytic Asymmetric Synthesis*; Ojima, I., Eds; WILEY-VCH: New York, 2000; pp 1-110. (b) *Transitions Metals for Organic Synthesis*; 2nd ed.; Beller, M., Bolm, C., Eds; WILEY-VCH: Weinheim, Germany, 2004. (c) *Handbook of Homogeneous Hydrogenation*; de Vries, J. G., Elsevier, C. J., Eds; WILEY-VCH: Weinheim, Germany, 2007.

[59] *Phosphorus Ligands in Asymmetric Catalysis*; 1st-3rd ed.; Börner, A., Eds; WILEY-VCH: Weinheim, Germany, 2008.

[60] (a) Takahashi, H.; Morimoto, T.; Achiwa, K. *Chem. Lett.* **1987**, *16*, 855-858. (b) Kitamura, M.; Ohkuma, T.; Inoue, S.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Ohta, T.; Takaya, H.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 629-631. (c) Mashima, K.; Kusano, K.-H.; Sato, N.; Matsumura, Y.-I.; Nozaki, K.; Kumobayashi, H.; Hori, Y.; Ishizaki, T.; Akutagawa, S.; Takaya, H. *J. Org. Chem.* **1994**, *59*, 3064-3076. (d) Benincori, T.; Brenna, E.; Sannicolò, F.; Trimarco, L.; Antognazzab, P.; Cesarotti, E. *J. Chem. Soc., Chem. Commun.* **1995**, 685-686. (e) Benincori, T.; Brenna, E.; Sannicolo, F.; Trimarco, L.; Antognazza, P.; Cesarotti, E.; Demartin, F.; Pilati, T. *J. Org. Chem.* **1996**, *61*, 6244-6251. (f) Naili, S.; Suisse, I.; Mortreux, A.; Agbossou, F.; Ali, M. A.; Karim, A. *Tetrahedron Lett.* **2000**, *41*, 2867-2870. (g) Boaz, N. W.; Debenham, S. D.; Mackenzie, E. B.; Large, S. E. *Org. Lett.* **2002**, *4*, 2421-2424. (h) Boaz, N. W.; Mackenzie, E. B.; Debenham, S. D.; Large, S. E.; Ponasik Jr, J. A. *J. Org. Chem.* **2005**, *70*, 1872-1880. (i) Qiu, L.; Kwong, F. Y.; Wu, J.; Lam, W. H.; Chan, S.; Yu, W.-Y.; Li, Y.-M.; Guo, R.; Zhou, Z.; Chan, A. S. C. *J. Am. Chem. Soc.* **2006**, *128*, 5955-5965. (j) Wang, C.-J.; Sun, X.; Zhang, X. *Synlett* **2006**, *2006*, 1169-1172. (k) Jahjah, M.; Alame, M.; Pellet-Rostaing, S.; Lemaire, M. *Tetrahedron: Asymmetry* **2007**, *18*, 2305-2312.

[61] Burk, M. J.; Kalberg, C. S.; Pizzano, A. *J. Am. Chem. Soc.* **1998**, *120*, 4345-4353.

[62] (a) Schäffner, B.; Holz, J.; Börner, A.; ThyssenKrupp Uhde GmbH; EP2141145, 2007. (b) Schäffner, B.; Andrushko, V.; Holz, J.; Verevkin, S. P.; Börner, A. *ChemSusChem* **2008**, *1*, 934-940.

[63] Leijondahl, K.; Borén, L.; Braun, R.; Bäckvall, J.-E. *Org. Lett.* **2008**, *10*, 2027-2030.

[64] Li, G.; Fronczek, F. R.; Antilla, J. C. *J. Am. Chem. Soc.* **2008**, *130*, 12216-12217.

[65] (a) Richter, A.; Kocienski, P.; Raubo, P.; Davies, D. E. *Anticancer Drug Des.* **1997**, *8*, 217-227. (b) Jiang, X.; Williams, N.; De Brabander, J. K. *Org. Lett.* **2007**, *9*, 227-230.

[66] (a) Tomita, F.; Takahashi, K.; Shimizu, K.-i. *J. Antibiot.* **1983**, 463-467. (b) Takahashi, K.; Tomita, F. *J. Antibiot.* **1983**, 468-470. (c) Tomita, F.; Takahashi, K.; Tamaoki, T. *J. Antibiot.* **1984**, 1268-1272. (d) Allan, K. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 17270-17271. (e) Wu, Y.-C.; Liron, M.; Zhu, J. *J. Am. Chem. Soc.* **2008**, *130*, 7148-7152.

[67] Mosey, R. A.; Floreancig, P. E. *Nat. Prod. Rep.* **2012**, *29*, 980-995.

[68] (a) Burres, N. S.; Clement, J. J. *Cancer Res.* **1989**, *49*, 2935-2940. (b) Venturi, V.; Davies, C.; Singh, A. J.; Matthews, J. H.; Bellows, D. S.; Northcote, P. T.; Keyzers, R. A.; Teesdale-Spittle, P. H. *J. Biochem. Mol. Toxicol.* **2012**, *26*, 94-100. (c) Lee, K.-H.; Nishimura, S.; Matsunaga, S.; Fusetani, N.; Horinouchi, S.; Yoshida, M. *Cancer Sci.* **2005**, *96*, 357-364.

[69] Perry, N. B.; Blunt, J. W.; Munro, M. H. G. *J. Am. Chem. Soc.* **1988**, *110*, 4850-4851.

[70] (a) Ogawara, H.; Higashi, K.; Uchino, K.; Perry, N. B. *Chem. Pharm. Bull. (Tokyo)* **1991**, *39*, 2152-2154. (b) Hood, K. A.; West, L. M.; Northcote, P. T.; Berridge, M. V.; Miller, J. H. *Apoptosis* **2001**, *6*, 207-219.

[71] Galvin, F.; Freeman, G. J.; Razi-Wolf, Z.; Benacerraf, B.; Nadler, L.; Reiser, H. *Eur. J. Immunol.* **1993**, *23*, 283-286.

[72] (a) Tsukamoto, S.; Matsunaga, S.; Fusetani, N.; Toh-e, A. *Tetrahedron* **1999**, *55*, 13697-13702. (b) Vuong, D.; Capon, R. J.; Lacey, E.; Gill, J. H.; Heiland, K.; Friedel, T. *J. Nat. Prod.* **2001**, *64*, 640-642.

[73] Troast, D. M.; Porco Jr, J. A. *Org. Lett.* **2002**, *4*, 991-994.

[74] (a) Sasaki, M.; Tsuda, M.; Sekiguchi, M.; Mikami, Y.; Kobayashi, J. i. *Org. Lett.* **2005**, *7*, 4261-4264. (b) Lai, D.; Brötz-Oesterhelt, H.; Müller, W. E. G.; Wray, V.; Proksch, P. *Fitoterapia* **2013**, *91*, 100-106.

[75] Harayama, Y.; Yoshida, M.; Kamimura, D.; Wada, Y.; Kita, Y. *Chem. Eur. J.* **2006**, *12*, 4893-4889.

[76] (a) Bates, R. W.; Boonsombat, J.; Lu, Y.; Nemeth, J. A.; Sa-Ei, K.; Song, P.; Peiling Cai, M.; Cranwell, P. B.; Winbush, S. *Pure Appl. Chem.* **2008**, *80*, 681-685. (b) Rech, J. C.; Floreancig, P. E. *Org. Lett.* **2003**, *5*, 1495-1498. (c) Huang, X.; Shao, N.; Palani, A.; Aslanian, R. *Tetrahedron Lett.* **2007**, *48*, 1967-1971. (d) Kiren, S.; Shangguan, N.; Williams, L. J. *Tetrahedron Lett.* **2007**, *48*, 7456-7459. (e) Wan, S.; Green, M. E.; Park, J.-H.; Floreancig, P. E. *Org. Lett.* **2007**, *9*, 5385-5388. (f) Ménard-Moyon, C.; Taylor, R. J. K. *Eur. J. Org. Chem.* **2007**, *2007*, 3698-3706. (g) Piri, F.; Moghaddama, M. B. F.; Karimi, B. *Electron. J. Chem.* **2007**, *4*, 519-522. (h) Ko, C.; Hsung, R. P. *Org. Biomol. Chem.* **2007**, *5*, 431-434.

[77] Vellalath, S.; Corić, I.; List, B. *Angew. Chem. Int. Ed.* **2010**, *49*, 9749-9752.

[78] (a) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356-5357. (b) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem. Int. Ed.* **2004**, *43*, 1566-1568.

[79] (a) Charles, I.; Latham, D. W. S.; Hartley, D.; Oxford, A. W.; Scopes, D. I. C. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1139-1146. (b) Dillard, R. D.; Easton, N. R. *J. Org. Chem.* **1966**, *31*, 2580-2584.

[80] Al-Awadi, N. A.; Al-Bashir, R. F.; El-Dusouqui, O. M. E. *J. Chem. Soc. Perk. Trans. 2* **1989**, 579-581.

[81] Pakrashi, S. C.; Chakravarty, A. K. *J. Org. Chem.* **1974**, *39*, 3828-3831.

[82] Lühr, S.; Holz, J.; Zayas, O.; Seidelmann, O.; Domke, L.; Börner, A. *Tetrahedron: Asymmetry* **2013**, *24*, 395-401.

[83] (a) *Enantioselective Synthesis of beta-Amino Acids*; Juaristi, E., Soloshonok, V. A.: Hoboken, New Jersey, 2005. (b) Abele, S.; Seebach, D. *Eur. J. Org. Chem.* **2000**, 1-15. (c) Porter, E. A.; Wang, X.; Lee, H.-s.; Weisblum, B. *Nature* **2000**, *404*, 2000-2000. (d) *Pseudo-Peptides In Drug Discovery*; Nielsen, P. E., Eds; WILEY-VCH: Weinheim, Germany, 2004.

[84] (a) Barrow, R. A.; Hemscheidt, T.; Liang, J.; Paik, S.; Moore, R. E.; Tius, M. A. *J. Am. Chem. Soc.* **1995**, *117*, 2479-2490. (b) Tius, M. A. *Tetrahedron* **2002**, *58*, 4343-4367. (c) Ding, Y.; Rath, C. M.; Bolduc, K. L.; Hakansson, K.; Sherman, D. H. *J. Am. Chem. Soc.* **2011**, *133*, 14492-14495.

[85] Eggen, M.; Georg, G. I. *Med. Res. Rev.* **2002**, *22*, 85-101.

[86] Nazaré, M.; Waldmann, H. *Angew. Chem.* **2000**, *112*, 1171-1174.

[87] Nazaré, M.; Waldmann, H. *Chem. Eur. J.* **2001**, *7*, 3363-3376.

[88] *Stereoselective Synthesis of Drugs and Natural Products*; Andrushko, V., Andrushko, N., Eds; WILEY-VCH: New York, 2013.

[89] Shustov, G. V.; Rauk, A. *Tetrahedron: Asymmetry* **1996**, *7*, 699-708.

[90] (a) Juaristi, E.; Quintana, D.; Balderas, M.; Garcia-Perez, E. *Tetrahedron: Asymmetry* **1996**, *7*, 2233-2246. (b) Agami, C.; Cheramy, S.; Dechoux, L.; Melaimi, M. *Tetrahedron* **2001**, *57*, 195-200. (c) Gutiérrez-Garcia, V. M.; Reyes-Rangel, G.; Munoz-Muniz, O.; Juaristi, E. *Helv. Chim. Acta* **2002**, *85*, 4189-4199. (d) Beddow, J. E.; Davies, S. G.; Ling, K. B.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2007**, *5*, 2812-2825.

[91] (a) Holz, J.; Zayas, O.; Jiao, H.; Baumann, W.; Spannenberg, A.; Monsees, A.; Riermeier, T. H.; Almena, J.; Kadyrov, R.; Börner, A. *Chem. Eur. J.* **2006**, *12*, 5001-5013. (b) Zhu, G.; Chen, Z.; Zhang, X. *J. Org. Chem.* **1999**, *64*, 6907-6910. (c) Heller, D.; Holz, J.; Drexler, H.-J.; Lang, J.; Drauz, K.; Krimmer, H.-P.; Börner, A. *J. Org. Chem.* **2001**, *66*, 6816-6817. (d) Holz, J.; Monsees, A.; Jiao, H.; You, J.; Komarov, I. V.; Fischer, C.; Drauz, K.; Börner, A. *J. Org. Chem.* **2003**, *68*, 1701-1707. (e) Reetz, M. T.; Li, X. *Angew. Chem. Int. Ed.* **2005**, *44*, 2959-2962. (f) Landert, H.; Spindler, F.; Wyss, A.; Blaser, H.-U.; Pugin, B.; Ribourduoille, Y.; Gschwend, B.; Ramalingam, B.; Pfaltz, A. *Angew. Chem. Int. Ed.* **2010**, *49*, 6873-6876. (g) Wu, Y.; Qi, S.-B.; Wu, F.-F.; Zhang, X.-C.; Li, M.; Wu, J.; Chan, A. S. C. *Org. Lett.* **2011**, *13*, 1754-1757. (h) Pignataro, L.; Boghi, M.; Civera, M.; Carboni, S.; Piarulli, U.; Gennari, C. *Chem. Eur. J.* **2012**, *18*, 1383-1400. (i) Imamoto, T.; Tamura, K.; Zhang, Z.; Horiuchi, Y.; Sugiya, M.; Yoshida, K.; Yanagisawa, A.; Gridnev, I. D. *J. Am. Chem. Soc.* **2012**, *134*, 1754-1769.

[92] Eilitz, U.; Leßmann, F.; Seidelmann, O.; Wendisch, V. *Tetrahedron: Asymmetry* **2003**, *14*, 189-191.

[93] (a) Saylik, D.; Campi, E. M.; Donohue, A. C.; Jackson, R. W.; Robinson, A. J. *Tetrahedron: Asymmetry* **2001**, *12*, 657-667. (b) Zupancic, B.; Mohar, B.; Stephan, M. *Org. Lett.* **2010**, *12*, 1296-1299. (c) Huang, H.; Liu, X.; Deng, J.; Qiu, M.; Zheng, Z. *Org. Lett.* **2006**, *8*, 3359-3362. (d) Deng, J.; Hu, X.-P.; Huang, J.-D.; Yu, S.-B.; Wang, D.-Y.; Duan, Z.-C.; Zheng, Z. *J. Org. Chem.* **2008**, *73*, 2015-2017. (e) Wieland, J.; Breit, B. *Nat. Chem.* **2010**, *2*, 832-837. (f) Guo, Y.; Shao, G.; Li, L.; Wu, W.; Li, R.; Li, J.; Song, J.; Qiu, L.; Prashad, M.; Kwong, F. Y. *Adv. Synth. Catal.* **2010**, *352*, 1539-1553. (g) Zupancic, B.; Mohar, B.; Stephan, M. *Org. Lett.* **2010**, *12*, 3022-3025. (h) Elaridi, J.; Thaqi, A.; Prosser, A.; Jackson, W. R.; Robinson, A. J. *Tetrahedron: Asymmetry* **2005**, *16*, 1309-1319. (i) Lühr, S.; Holz, J.; Zayas, O.; Wendisch, V.; Börner, A. *Tetrahedron: Asymmetry* **2012**, *23*, 1301-1319.

[94] (a) Yu, C.; Liu, B.; Hu, L. *J. Org. Chem.* **2001**, *66*, 5413-5418. (b) Aranha, R. M.; Bowser, A. M.; Madalengoitia, J. S. *Org. Lett.* **2009**, *11*, 575-578.

[95] (a) Basavaiah, D.; Satyanarayana, T. *Chem. Commun. (Camb.)* **2004**, 32-33. (b) Hoen, R.; Tiemersma-Wegman, T.; Procuranti, B.; Lefort, L.; de Vries, J. G.; Minnaard, A. J.; Feringa, B. L. *Org. Biomol. Chem.* **2007**, *5*, 267-275.

[96] (a) Kippo, T.; Fukuyama, T.; Ryu, I. *Org. Lett.* **2011**, *13*, 3864-3867. (b) Tong, X.; Lai, J.; Guo, B.-H.; Huang, Y. *J. Polym. Sci. A Polym. Chem.* **2011**, *49*, 1513-1516.

[97] (a) Huck, J.; Duru, C.; Roumestant, M. L.; Martinez, J. *Synthesis* **2003**, *2003*, 2165-2168. (b) Huck, J.; Receveur, J.-M.; Roumestant, M.-L.; Martinez, J. *Synlett* **2001**, *2001*, 1467-1469.

[98] Takagi, M.; Yamamoto, K. *Tetrahedron* **1991**, *47*, 8869-8882.

[99] Brown, P.; Southgate, R. *Tetrahedron Lett.* **1986**, *27*, 247-250.

[100] (a) Moonen, K.; Laureyn, I.; Stevens, C. V. *Chem. Rev.* **2004**, *104*, 6177-6215. (b) Xu, B.; Hammond, G. B. *Angew. Chem.* **2005**, *117*, 7570-7573. (c) Palacios, F.; Alonso, C.; de Los Santos, J. M. *Chem. Rev.* **2005**, *105*, 899-931. (d) Ma, J.-A. *Chem. Soc. Rev.* **2006**, *35*, 630-636.

[101] (a) Ibrahem, I.; Hammar, P.; Vesely, J.; Rios, R.; Eriksson, L.; Córdova, A. *Adv. Synth. Catal.* **2008**, *350*, 1875-1884. (b) Ibrahem, I.; Rios, R.; Vesely, J.; Hammar, P.; Eriksson, L.; Himo, F.; Córdova, A. *Angew. Chem.* **2007**, *119*, 4591-4594. (c) Carlone, A.; Bartoli, G.; Bosco, M.; Sambri, L.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2007**, *46*, 4504-4506. (d) Chen, Y.-R.; Duan, W.-L. *Org. Lett.* **2011**, *13*, 5824-5826.

[102] Henry, J. C.; Lavergne, D.; Ratovelomanana-Vidal, V.; Genêt, J. P. *Tetrahedron Lett.* **1998**, *39*, 3473-3476.

[103] Dong, K.; Wang, Z.; Ding, K. *J. Am. Chem. Soc.* **2012**, *134*, 12474-12477.

[104] Cheruku, P.; Paptchikhine, A.; Church, T. L.; Andersson, P. G. *J. Am. Chem. Soc.* **2009**, *131*, 8285-8289.

[105] Uozumi, Y.; Tanahashi, A.; Lee, S.-Y.; Hayashi *J. Org. Chem.* **1993**, *58*, 1945-1948.

[106] Kabat, M. M.; Garofalo, L. M.; Daniewski, a. R.; Hutchings, S. D.; Liu, W.; Okabe, M.; Radinov, R.; Zhou, Y. *J. Org. Chem.* **2001**, *66*, 6141-6150.

[107] Korostylev, A.; Selent, D.; Monsees, A.; Borgmann, C.; Börner, A. *Tetrahedron: Asymmetry* **2003**, *14*, 1905-1909.

[108] Straub, B. F.; Wrede, M.; Schmid, K.; Rominger, F. *Eur. J. Inorg. Chem.* **2010**, *2010*, 1907-1911.

[109] van der Vlugt, J. I.; Hewat, A. C.; Neto, S.; Sablong, R.; Mills, A. M.; Lutz, M.; Spek, A. L.; Müller, C.; Vogt, D. *Adv. Synth. Catal.* **2004**, *346*, 993-1003.

[110] (a) Piras, I.; Jennerjahn, R.; Jackstell, R.; Baumann, W.; Spannenberg, A.; Franke, R.; Wiese, K.-D.; Beller, M. *J. Organomet. Chem.* **2010**, *695*, 479-486. (b) Mikhel, I. S.; Dubrovina, N. V.; Shuklov, I. A.; Baumann, W.; Selent, D.; Jiao, H.; Christiansen, A.; Franke, R.; Börner, A. *J. Organomet. Chem.* **2011**, *696*, 3050-3057.

[111] Pàmies, O.; Diéguez, M. *Chem. Eur. J.* **2008**, *14*, 944-960.

[112] (a) Diéguez, M.; Ruiz, A.; Claver, C. *Tetrahedron: Asymmetry* **2001**, *12*, 2827-2834. (b) Raluy, E.; Claver, C.; Pàmies, O.; Diéguez, M. *Org. Lett.* **2007**, *9*, 49-52. (c) Diéguez, M.; Ruiz, A.; Claver, C. *Tetrahedron: Asymmetry* **2001**, *12*, 2861-2866.

[113] Kartha, K. P. R. *Tetrahedron Lett.* **1986**, *27*, 3415-3416.

[114] (a) *Stereochemistry of Carbon Compounds*; Eliel, E. L., Wilen, S. H., Eds; McGraw Hill Book Company: New York, 1962. (b) Aksnes, G.; Albriktsen *Acta Chem. Scand.* **1965**, *19*, 920-930.

[115] Tipson, S. R.; Isbell, H. S.; Stewart, J. E. *J. Res. Natl. Bur. Stand.* **1959**, *62*, 257-282.

[116] Loh, W.; Chevron Research Company; US4554010, 1984.

[117] Jin, Y.; Just, G. *J. Org. Chem.* **1998**, *63*, 3647-3654.

[118] Nakano, H.; Yokoyama, J.-I.; Fujita, R.; Hongo, H. *Tetrahedron Lett.* **2002**, *43*, 7761-7764.

[119] Aikawa, K.; Mikami, K. *Chem. Commun. (Camb.)* **2012**, *48*, 11050-11069.

[120] (a) Buisman, G. J. H.; Martin, M. E.; Vos, E. J.; Klootwijk, A.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Tetrahedron: Asymmetry* **1995**, *6*, 719-738. (b) van der Slot, S. C.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Fraanje, J.; Goubitz, K.; Lutz, M.; Spek, A. L. *Organometallics* **2000**, *19*, 2504-2515. (c) Diéguez, M.; Pàmies, O.; Ruiz, a.; Castillón, S.; Claver, C. *Chem. Eur. J.* **2001**, *7*, 3086-3094.

[121] Shulgina, G. I. *Pavlov. J. Biol. Sci.* **1986**, *21*, 129-140.

[122] (a) Mezler, M.; Müller, T.; Raming, K. *Eur. J. Neurosci.* **2001**, *13*, 477-486. (b) Dzitoyeva, S.; Dimitrijevic, N.; Manev, H. *Proc. Natl. Acad.Sci. USA* **2003**, *100*, 5485-5490.

[123] (a) Wachtel, H. *Neuropharmacology* **1983**, *22*, 267-272. (b) Bobon, D.; Breulet, M.; Gerad-Vandenhove, M. A.; Guiot-Goffioul, F.; Plomteux, G.; Sastre-y-Hermández, M.; Schratzer, M.; Troisfontaines, B.; von Frenckell, R.; Wachtel, H. *Eur. Arch. Psychiatry Neurol. Sci.* **1988**, *238*, 2-6. (c) Zhu, J.; Mix, E.; Winblad, B. *CNS Drug Rev.* **2001**, *7*, 387-398.

[124] (a) Maxwell, C. R.; Kanes, S. J.; Abel, T.; Siegel, S. J. *Neuroscience* **2004**, *129*, 101-107. (b) Kanes, S. J.; Tokarczyk, J.; Siegel, S. J.; Bilker, W.; Abel, T.; Kelly, M. P. *Neuroscience* **2007**, *144*, 239-246.

[125] Sommer, N.; Löschmann, P. A.; Northoff, G. H.; Weller, M.; Steinbrecher, A.; Steinbach, J. P.; Lichtenfels, R.; Meyermann, R.; Riethmüller, A.; Fontana, A. *Nat. Med.* **1995**, *1*, 244-248.

[126] (a) Semmler, J.; Wachtel, H.; Endres, S. *Int. J. Immunopharmacol* **1993**, *15*, 409-413. (b) Chen, T. C.; Wadsten, P.; Su, S.; Rawlinson, N.; Hofman, F. M.; Hill, C. K.; Schönthal, A. H. *Cancer Biol. Ther.* **2002**, *1*, 268-276.

[127] Ahlbrecht, H.; Bonnet, G.; Enders, D.; Zimmermann, G. *Tetrahedron Lett.* **1980**, *21*, 3175-3178.

[128] Mukaiyama, T.; Hayashi, H.; Miwa, T.; Narasaka, K. *Chem. Lett.* **1982**, 1637-1640.

[129] (a) Hashimoto, S.-I.; Yamada, S.-I.; Koga, K. *Chem. Pharm. Bull. (Tokyo)* **1979**, *27*, 771-782. (b) Tomioka, K.; Shindo, M.; Koga, K. *J. Am. Chem. Soc.* **1989**, *111*, 8266-8268. (c) Shindo, M.; Koga, K.; Tomioka, K. *J. Org. Chem.* **1998**, *63*, 9351-9357.

[130] Mangeney, P.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1986**, *27*, 3143-3146.

[131] (a) Besace, Y.; Berlan, J.; Pourcelot, G.; Huche, M. *J. Org. Chem.* **1983**, *247*, 11-13. (b) Berlan, J.; Besace, J.; Stephan, E.; Cresson, P. *Tetrahedron Lett.* **1985**, *26*, 5765-5768. (c) Berlan, J.; Besace, Y. *Tetrahedron* **1986**, *42*, 4767-4776.

[132] Palais, L.; Babel, L.; Quintard, A.; Belot, S.; Alexakis, A. *Org. Lett.* **2010**, *12*, 1988-1991.

[133] (a) Tanaka, K.; Qiao, S.; Tobisu, M.; Lo, M. M.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 9870-9871. (b) Tanaka, K.; Fu, G. C. *J. Org. Chem.* **2001**, *66*, 8177-8186.

[134] Arai, N.; Sato, K.; Azuma, K.; Ohkuma, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 7500-7504.

[135] (a) Mantilli, L.; Gérard, D.; Torche, S.; Besnard, C.; Mazet, C. *Angew. Chem. Int. Ed.* **2009**, *48*, 5143-5147. (b) Li, J.-Q.; Peters, B.; Andersson, P. G. *Chem. Eur. J.* **2011**, *17*, 11143-11145.

[136] (a) Yang, J. W.; Hechavarria Fonseca, M. T.; Vignola, N.; List, B. *Angew. Chem. Int. Ed.* **2004**, *44*, 108-110. (b) Zhao, G.-L.; Córdova, A. *Tetrahedron Lett.* **2006**, *47*, 7417-7421. (c) MacMillan, D.; Ouellet, S.; Tuttle, J.; California Institute Of Technology; US20080125310, 2006. (d) Akagawa, K.; Akabane, H.; Sakamoto, S.; Kudo, K. *Org. Lett.* **2008**, *10*, 2035-2037. (e) Maeda, H.; Hori, Y.; Takasago International Corporation; WO2010140636, 2010. (f) Ebner, C.; Pfaltz, A. *Tetrahedron* **2011**, *67*, 10287-10290.

[137] Ouellet, S. G.; Tuttle, J. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 32-33.

[138] (a) Kanazawa, Y.; Nishiyama, H. *Synlett* **2006**, *2006*, 3343-3345. (b) Maeda, H.; Yamada, S.; Itoh, H.; Hori, Y. *Chem. Commun. (Camb.)* **2012**, *48*, 1772-1774.

[139] Hock, H.; Lang, S. *Ber. Dtsch. Chem. Ges.* **1944**, *77*, 257-264.

[140] Hoffman, R. V.; Johnson, M. C.; Okonya, J. F. *J. Org. Chem.* **1997**, *62*, 2458-2465.

[141] Nuñez, S. A.; Yeung, K.; Fox, N. S.; Phillips, S. T. *J. Org. Chem.* **2011**, *76*, 10099-10113.

[142] Pautigny, C.; Jeulin, S.; Ayad, T.; Zhang, Z.; Genêt, J.-P.; Ratovelomanana-Vidal, V. *Adv. Synth. Catal.* **2008**, *350*, 2525-2532.

[143] Janecki, T.; Wasek, T.; Olczak, J. *Synlett* **2006**, *2006*, 1507-1510.

[144] Salamonczyk, G. M.; Han, K.; Guo, Z.-w.; Sih, C. J. *J. Org. Chem.* **1996**, *61*, 6893-6900.

[145] Zhang, X.; Cao, B.; Yu, S.; Zhang, X. *Angew. Chem. Int. Ed.* **2010**, *49*, 4047-4050.

[146] Wang, D.-Y.; Hu, X.-P.; Deng, J.; Yu, S.-B.; Duan, Z.-C.; Zheng, Z. *J. Org. Chem.* **2009**, *74*, 4408-4410.

[147] Kawaguchi, S.-i.; Nagat, S.; Nomoto, A.; Sonoda, M.; Ogawa, A. *J. Org. Chem.* **2008**, *73*, 7928-7933.

[148] Baker, M. J.; Pringle, P. G. *J. Chem. Soc., Chem. Commun.* **1991**, 1292-1293.

[149] Ferreira, S. B.; Sodero, A. C. R.; Cardoso, M. F. C.; Lima, E. S.; Kaiser, C. R.; Silva Jr, F. P.; Ferreira, V. F. *J. Med. Chem.* **2010**, *53*, 2364-2375.

[150] Cho, B. T.; Kim, N. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2901-2907.

[151] Denmark, S. E.; Amishiro, N. *J. Org. Chem.* **2003**, *68*, 6997-7003.

[152] Iwama, T.; Ogawa, M.; Kataoka, T.; Muraoka, O.; Tanabe, G. *Tetrahedron* **1998**, *54*, 8941-8974.

[153] Cahiez, G.; Foulgoc, L.; Moyeux, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 2969-2972.